Non-Invasive Measurement of Breathing Patterns using the Respiratory Inductive Plethysmograph.

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To Mairi

Formal Declaration

I declare that I have written this dissertation presented to the University of Edinburgh for the degree of Doctor of Medicine; that it is based upon my own observations and that, except as indicated in the thesis, the data was collected, analysed and interpreted by me.

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ABSTRACT OF THESIS (Regulation 7.9)

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Variation in airway calibre produces changes in respiratory drive. This change in respiratory drive may be studied by analysis of breathing pattern. Respiratory patterns in the acute clinical setting are rarely recorded. However, would this provide clinically important information? Masks and mouthpieces are not well tolerated by acutel distressed patients and alters breathing pattern, thus measurements of respiratory timing and ventilation have been carried out using the respiratory inductive plethysmograph.

To correlate the changes in breathing pattern with changes in airway calibre, two groups of patients were studied - one group who had variable airways obstruction, that is asthma and the other group who had fixed airways obstruction - chronic bronchitis and emphysema. Patients who bronchodilated in treatment, i.e. asthmatic patients, showed falls in tidal volume, inspiratory drive and ventilation. Patients with chronic bronchitis and emphysema whose peak expiratory flow rate did not change showed no change in breathing pattern. To investigate whether bronchodilation itself caused changes in breathing pattern, patients admitted with acute asthma were given either Terbutaline, or Ipratropium or a combination of both drugs. Again there were similar falls in tidal volume, inspiratory drive and ventilation, and there were no differences between treatments. Thus bronchodilatation alone caused the changes observed. Furthermore in 10 patients whose peak expiratory flow rate did not change significantly, but who were clinically improving, similar changes in breathing pattern were recorded.

If the changes occur with the bronchodilatation, are reciprocal changes produced with bronchoconstriction? Thus 10 stable asthmatic patients were challenged with either histamine or methacholine to induce bronchoconstriction. Increase in expiratory time, breath period and fall in ventilation were found, with a fall in ear oxygen saturation, which were reversed by a $beta_2$ agonist. No such changes occurred with methacholine.

In order to study the effect of spontaneous bronchoconstriction in asthma, patients with nocturnal asthma were studied overnight. All patients bronchoconstricted but when comparable sleep stages were analysed, no changes in breathing pattern were observed.

Thus the respiratory inductive plethysmograph allows recording of changes in breathing pattern which can be related to changes in airway calibre. Moreover this technique is patient acceptable. Changes in breathing pattern may be seen before changes in peak expiratory flow rate. Indirectly induced broncho constriction produced different change in breathing pattern to that of acute asthma, and no changes were seen in breathing pattern, in nocturnal asthma. This inconsistency may be reflected in the severity of bronchoconstriction or in differences in the mechanisms of induction or bronchoconstricti

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CHAPTER 1

Introduction

Respiratory disease accounts for a large proportion of death and disability in the United Kingdom (Crofton and Douglas, 1981). Black and Pole (1975) have attempted to calculate the "burden" of different categories of disease in Britain, in order to identify those requiring a greater concentration of biomedical research. They found that respiratory disease, with a burden calculated as 13.47% came second only to mental disease and handicap at 13.60%, with the next highest group, ischaemic heart disease at 6.59%, a long way third. Furthermore, nearly a fifth of all consultations in general practice in Britain are for respiratory disease (Royal College of General Practitioners, 1979) [Fig 1]. Although lung cancer accounts for the commonest cause of respiratory death, the disease of chronic bronchitis and emphysema, and asthma, account for a sizeable proportion of respiratory mortality and morbidity.

Chronic bronchitis and emphysema is the commonest cause of loss of work in Britain, accounting for the vast majority of the 30 million working days lost each year in Britain from chronic respiratory disease (Office of Health Economics, 1977). Chronic bronchitis is

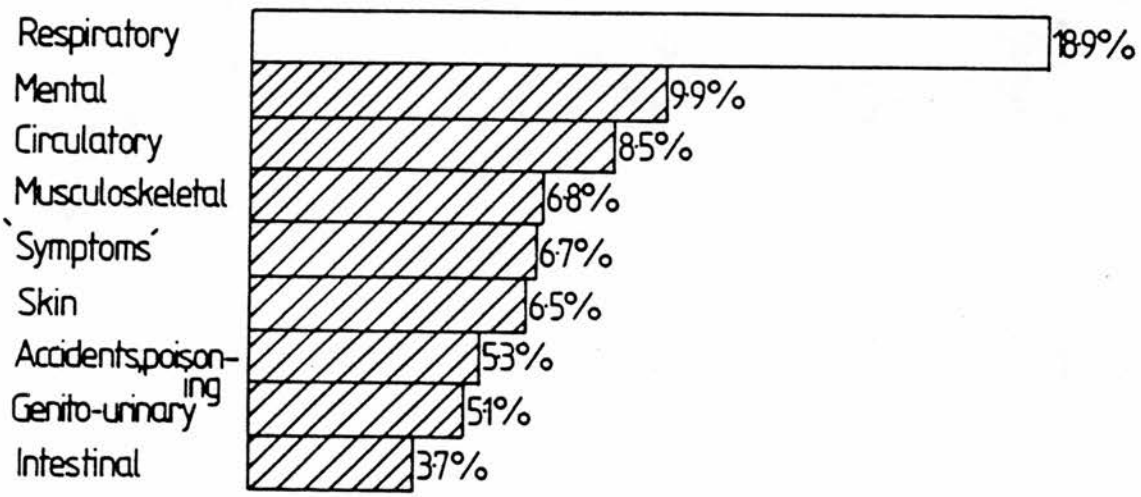

Figure 1 Principal conditions for which general practitioners were consulted in Britain. Only the larger diagnostic groups have been included. Figures are from the National Morbidity Survey 1970-71.

defined as an increase in mucus production by the lower respiratory tract, presenting clinically as persistent cough with sputum production for more than three months in each year over the previous three years (Medical Research Council, 1965). Emphysema is defined in pathological terms as an increase beyond normal in the size of the airspaces distal to the terminal bronchioles with destruction of their walls. It is thus difficult to diagnose both clinically and radiologically (Thurlbeck and Simon, 1978), however the introduction of computerised axial tomography (CT scanning) has now made this possible during life (Hayhurst et al, 1985).

Chronic bronchitis and emphysema is far commoner in men and a survey amongst representative general practices throughout Britain (College of General Practitioners, 1961) showed that 17% of all men and 8% of all women aged between 40 and 64 years had clinical symptoms of chronic bronchitis and emphysema.

Asthma is usually defined as recurrent generalised airways obstruction, which at least in its early stages is paroxysmal and reversible. It is associated with marked breathlessness and wheeze and compared to morbidity however, the mortality is low. Asthma mortality rose sharply in the 1960's in several countries, including England and Wales (Morrison Smith, 1966; Fraser and Doll, 1971), being greatest in the 5-34 age group. There has been no satisfactory explanation for this, but the parallel changes in asthma mortality

and the pattern of aerosol sales in several countries, seemed to implicate the increased use of isoprenaline inhalers (Inman and Adelstein; 1969, Stolley, 1972). The mortality seemed to decline but a further epidemic of deaths in Australia and New Zealand (Jackson et al, 1982) stimulated fresh interest in the diagnosis and management of asthma. The asthma death rate rose from 1.3 per 100,000 in 1974 to 4.1 per 100,000 in 1979 and there are preliminary indications that the death rate from asthma may also be rising in the United States (Sly, 1984). Furthermore, recent reports suggest that in the UK mortality rose annually by an average 4.7% in the 5-34 age group and among males 6.1% per annum, and this increased mortality since 1974 has probably accounted for 408 excess deaths (Burney, 1986). No satisfactory explanation for this rise in mortality is forthcoming.

Asthma has been classified as a condition amenable to treatment (Rutstein et al, 1976) and thus suitable as a marker of the quality of the health services. In many countries (Charlton and Velez, 1986) deaths from diseases classified as being amenable to treatment have declined considerably over the past two to three decades, except for asthma. With this worrying upward trend in the mortality of asthma there is no room for complacency. Further research is required in an attempt to reverse this trend in mortality and to improve morbidity.

Measurement of breathing pattern

The spirometer has been used in clinical practice for well over a century. It is a simple yet effective device, however, in his original description of the spirometer Hutchinson (1844) cautioned that errors might arise with instruments requiring the use of a mouthpiece. Conventional methods of measuring ventilation have depended upon breathing through a mouthpiece, with the nose being occluded by a noseclip, connected to a spirometer or pneumotachograph. In 1960 Mead noted the difference in respiratory frequency when measured in subjects unaware of being observed at a public meeting (17 breaths per minute) compared to recordings obtained on a respiratory apparatus (12 breaths per minute).

Gilbert and co-workers (1972) were the first to demonstrate that breathing on a mouthpiece with a noseclip applied, not only caused frequency (f) to fall but also induced an increase in tidal volume (Vt). Several reasons have been put forward for this. Irritation and stimulation of the nasal mucosa depressed the respiratory frequency in both man and lower animals (Anderson, 1954; Gesell and Hamilton, 1941; and Koisumi et al, 1961). Trigeminal nerve stimulation in rabbits has been shown to exert considerable influence over brain stem output to the respiratory and cardiovascular systems (Anderson, 1954; Kumada et al, 1977).

Stimulation of the nasal and upper airway receptors in cats has been shown to slow frequency (Boushey et al, 1972; Sasaki et al, 1975) and increase Vt (Boushey et al, 1972). In human infants, facial stimulation with a mask rim firmly applied around the nose caused a significant increase in Vt and a fall in frequency (Dolfin et al, 1983).

Thus it seems likely that the fall in respiratory frequency produced by the respiratory apparatus may be related to the irritating affects of the nose clip and mouthpiece on the nasal and oral mucosa. If so, the rise in tidal volume could be considered secondary and serves to maintain adequate ventilation. This, however, is further complicated, as anxiety has been shown to increase frequency (Bechbache et al, 1979; Rigg et al, 1977) and this might cancel the slowing expected with sensory receptor stimulation.

In addition to causing nasal and oral stimulation, employment of a mouthpiece and noseclip produces obligatory oral breathing. This shift from nasal to oral breathing, that is a change in breathing route rather than instrumentation, was suggested by Douglas et al (1983) for being responsible for the changes in breathing pattern. Previously however, Hirsch and Bishop (1982) had dismissed this hypothesis. However, more recently, studies by Perez and Tobin (1985) and Rodenstein et al (1985) are in agreement with Douglas and co-workers, in that it is the breathing route which

is important as one of the factors in changing the pattern of breathing. Rodenstein et al (1985) showed that mouth opening but without oral flow i.e. nasal breathing, induces no change whatever in the resting breathing pattern. On the other hand, mouth breathing, even without connection to a respiratory device induces the same changes in breathing pattern as breathing through a mouthpiece and noseclip. Thus it is concluded, that it is not breathing through a mouthpiece or noseclip that modified the respiratory pattern, but the obligatory oral route thus imposed.

The increased tidal volume has been repeatedly confirmed but controversy exists as to whether the respiratory apparatus alters frequency and the subsets of respiratory timing (Gilbert et al, 1972; Hirsch and Bishop, 1982; Sackner et al, 1980) or affects respiratory drive and overall minute ventilation (Douglas et al, 1983; Weismann et al, 1984). This is obviously important because if use of a mouthpiece and noseclip (or oral breathing route) alters both the volume and time components of the respiratory cycle, it markedly limits the value of breathing pattern data obtained in this way. Furthermore, for obvious reasons, acutely distressed patients are unable to tolerate such devices and thus studies of ventilation and breathing pattern in the acute clinical setting are sparse.

The subsequent introduction of techniques that can

measure ventilation without physical connection to the airway, has enabled measurement of breathing pattern in man, at rest and in various disease states, possible and eliminates the difficulties previously encountered with masks and mouthpieces.

Changes in airway calibre may produce detectable changes in breathing pattern, and if so, may provide important clinical information. This information may help to indicate patients who are developing potentially fatal asthmatic attacks, and thus appropriate treatment can be initiated to prevent this. Careful monitoring of breathing patterns during an acute attack, may provide further useful clinical information as to the response to treatment, and thus ensure a safe and full recovery for the patient.

Normal Respiratory Motion

The chest wall can be divided into three parts: the diaphragm, the rib cage with its musculature, and the abdomen with its musculature (Roussos and Macklem, 1982). External breathing movements take place through one of two pathways: displacement of the abdominal wall or the rib cage (Konno and Mead, 1967; Konno and Mead, 1968; Grimby et al, 1968; Sharp et al, 1974). The sum of the volumes displaced by the abdominal wall and the rib cage is for practical purposes the total volume change of the throacic cavity, which must equal the volume change of the lung. Forces developed by the

inspiratory muscles act on the abdomen and rib cage to displace them and to increase lung volume.

In the normal person the inspiratory muscles can be functionally divided into a) the diaphragm and b) external intercostal and accessory muscles. The diaphragm itself has two functionally distinct components: the costal and the crural parts (De Troyer et al, 1981). When the costal part of the diaphragm contracts, the dome displaces the abdominal viscera downwards. To the extent that the viscera resist being displaced, the costal fibres develop a force on the rib cage, which lifts it. Thus, costal diaphragmatic contraction displaces both the rib cage and the abdomen while inflating the lung. Contraction of the crural part of the diaphragm, because it lacks attachment to the rib cage, only displaces the abdomen while it inflates the lungs (De Troyer, 1981). The diaphragm is directly in contact with a portion of the inner aspect of the rib cage designated the "zone of apposition" (Mead, 1979) and direct transmission of abdominal pressure to this area results in rib cage expansion. Since the two parts of the diaphragm have different segmental innervation (Sant' Ambrogio et al 1963), different actions and different embryological and evolutionary origins (Langman, 1978), they can appropriately be regarded as two separate muscles.

Contraction of the external intercostal muscles or

accessory muscles of inspiration (or both) produces expansion of the rib cage. If inspiration is performed entirely with intercostal or accessory muscles, with the diaphragm remaining relaxed (say, as in phrenic nerve paralysis), the fall in pleural pressure required to inflate the lung is transmitted to the abdomen across the flaccid diaphragm. Under these conditions, in contrast with diaphragmatic contraction, abdominal pressure falls, and the abdomen is displaced inward instead of outward. Because the change in lung volume is the sum of the displacement of the rib cage and abdomen, the volume displaced by the rib cage will be greater than the change in the volume of the lung by an amount equal to the change in the volume displaced by the abdomen. Thus it is apparent that breathing with the intercostal or accessory muscles alone is most inefficient (Konno and Mead, 1967; Grimby et al, 1976; Goldman et al, 1976) and does not normally occur. Goldman and Mead (1973) hypothesised that the diaphragm was the only importantly active respiratory muscle in the erect posture, and its action alone could drive both the rib cage and abdomen. In support of this Grimby et al (1976) used magnetometers to study the use of respiratory muscles during quiet breathing and hyperpnea induced by exercise and rebreathing. They concluded that abdominal muscles are relaxed at rest and that they become active only when ventilation increases. This hypothesis for events is no longer accepted (Campbell

and Green, 1955; Loring et al, 1982). Loring and co-workers (1982) have shown that during quiet breathing most subjects showed evidence of tonic or phasic abdominal muscle contraction while standing or sitting but not supine. Subjects studied during hyperpnea immediately following exercise showed evidence of greater abdominal muscle contraction than at rest.

In 1967 Konno and Mead suggested that the respiratory system could be regarded as a simple physical system with two independent moving parts - the rib cage and abdomen. They argued that volume change at the mouth is equal to the sum of the volume change of the rib cage and abdominal compartments and thus it could be said that the respiratory system possesses two degrees of freedom of motion.

The contribution of the rib cage and abdomen to tidal breathing varies with posture. In the erect position, most subjects breath predominantly with rib cage expansion, approximately two thirds rib cage and one third abdominal expansion (Sharp et al, 1975). This contribution is reversed in the supine position [Fig 2]. A combination of factors is thought to account for this postural variation. The relative compliance of the rib cage and abdomen vary with posture, that is, it is reduced on standing (Konno and Mead, 1968). The muscles of the anterolateral wall of the abdomen are used mainly for the compression of the abdominal contents. The

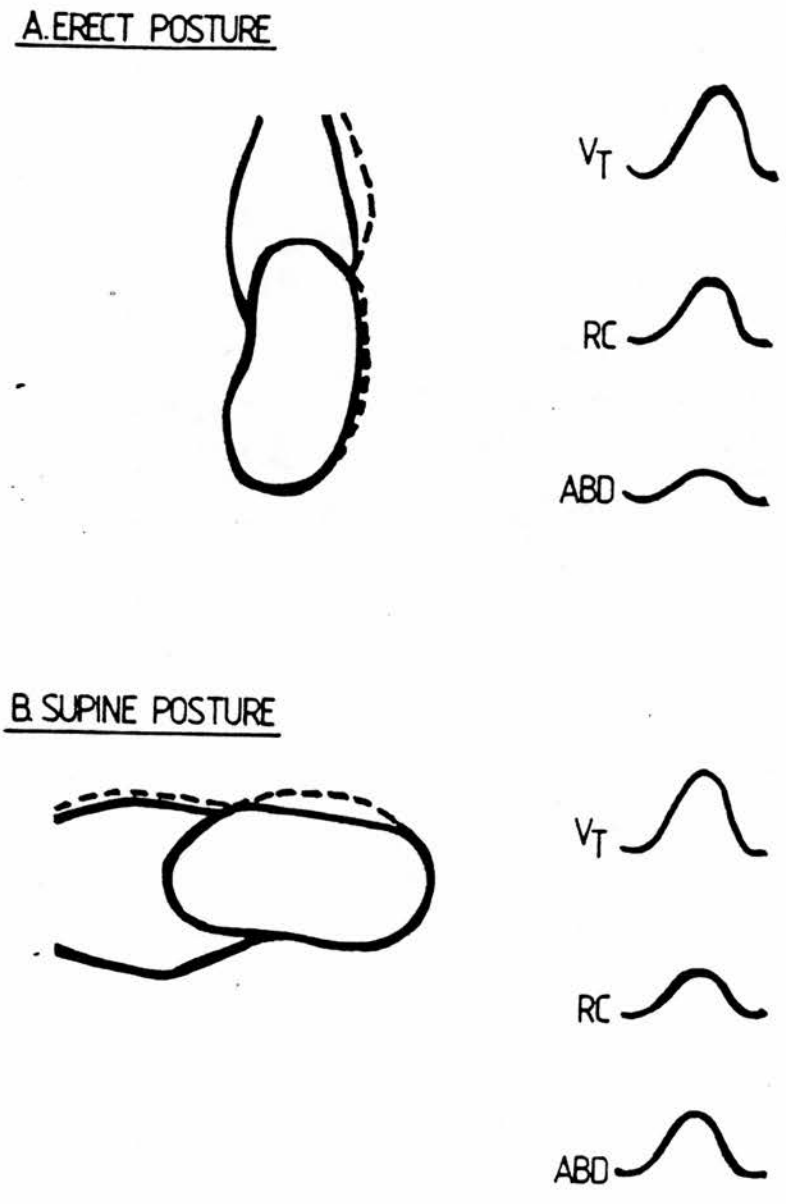

Figure 2 Abdomen and chest wall movement.
_____ end expiration
--------- end inspiration

anatomical attachments and muscle fibre orientation suggest that they act to pull down the ribs. For these reasons the abdominal muscles have traditionally been considered to be expiratory (Agostini and Campbell, 1970). However, this has now been challenged (De Troyer et al, 1983). These authors have shown that the abdominal muscles have two opposing actions on the rib cage when they contract. The net effect of these muscles depends on the balance between the force related to the muscle insertions, which tends to deflate the rib cage and the rise in abdominal pressure, which operating by way of the area of apposition and passive distension of the diaphragm tends to inflate the lower rib cage (De Troyer et al, 1983). Differences in the sites of rib cage attachment and muscle fibre orientation are thought to account for the fact that different muscles of the abdominal wall have different effects on the rib cage. That the muscles of the abdominal wall contribute to breathing in man is borne out by electromyographic (EMG) studies showing the coordinated use of different abdominal muscles (Druz and Sharp, 1981; Strohl et al, 1981).

For many years it was considered that women displayed a different pattern of breathing from men, in that costal respiration predominated in the female and abdominal breathing was characteristic of the male. Sharp et al (1975) have shown this not to be the case.

Using magnetometers to produce a quantitative measure of compartmental excursion they demonstrated similar rib cage and abdominal motion in both sexes.

The muscles of the rib cage, abdomen and diaphragm are now considered to be a coordinated unit (Crawford et al, 1983; McCool et al, 1985) interacting with each other to produce normal tidal breathing. From the concept of Konno and Mead (1967) that the respiratory system operates with 2 degrees of freedom, that is by recording motion of the rib cage and abdomen, this can provide a measure of ventilatory performance.

The Control of Breathing

The movements of breathing involve the complex interaction of chemical, neural, muscular and mechanical processes. Thus it is remarkable that normal individuals can maintain blood gas tensions and pH within a narrow range. Even more surprising is that patients who exhibit a variety of respiratory disease still can maintain almost normal blood gases. However, with severe disease this ability is lost and an increased resting arterial P_{CO_2} ($PaCO_2$) beyond normal limits indicates breakdown of the control system of breathing producing Ventilatory Failure.

Whilst ventilatory failure is easy to ascertain by simple measurement of resting arterial P_{CO_2} it must be

remembered that the basic aspects of control of breathing are not yet fully understood. Nevertheless, the recent advances in the control of breathing have resulted in the development of simple non-invasive methods which are useful for clinical testing.

Clinical Methods used in the evaluation of Control of Breathing

Methods used in the control of breathing have been based on measurement of the ventilatory response to CO_2 (Read, 1967) hypoxia (Rebuck and Campbell, 1974) and exercise. Whilst study of these responses provides useful information, of greater benefit is assessing control of breathing at rest. Thus having defined ventilatory failure in terms of an increase $PaCO_2$ during air breathing at rest, it is of great interest to explain how this is brought about.

The arterial Pco_2 is given by the ratio of metabolic CO_2 production (Vco_2) to alveolar ventilation, and can be expressed in the following form:

$$PaCO2 = \frac{VCO2 \times k}{VE\ (1-VD/Vt)} \qquad \text{Equation 1}$$

where k is a constant

VE is minute ventilation

Vt is tidal volume

VD is physiological dead space.

The latter is computed by direct measurement of the other variables in Equation 1. Thus Equation 1 reveals that the breathing pattern plays an important role in determining $PaCO_2$ that is for a given VE and VD the alveolar ventilation will decrease the smaller Vt (and hence the higher the respiratory frequency).

Analysis of the breathing pattern

The respiratory cycle consists of a phase of increasing lung volume - inspiration and a descending limb - expiration [Fig 3]. It can be shown diagramatically as the volume displaced Vt, duration of inspiration (Ti) duration of expiration (Te) and total cycle duration (Ttot) or breath period. Classically, breathing pattern was analysed in terms of tidal volume and respiratory frequency (f) but this provides only limited information and does not indicate the mechanisms which affect Vt and f. The tidal volume can be altered by a change in the rate of rise of lung volume (inspiratory flow) or by a change in Ti, or both.

$$\text{Similarly, } f = \frac{1}{\overline{T}tot}$$

$$\text{which in turn} = \frac{1}{(\overline{T}i + Te)}$$

and thus f can be altered by changes in Ti or Te.

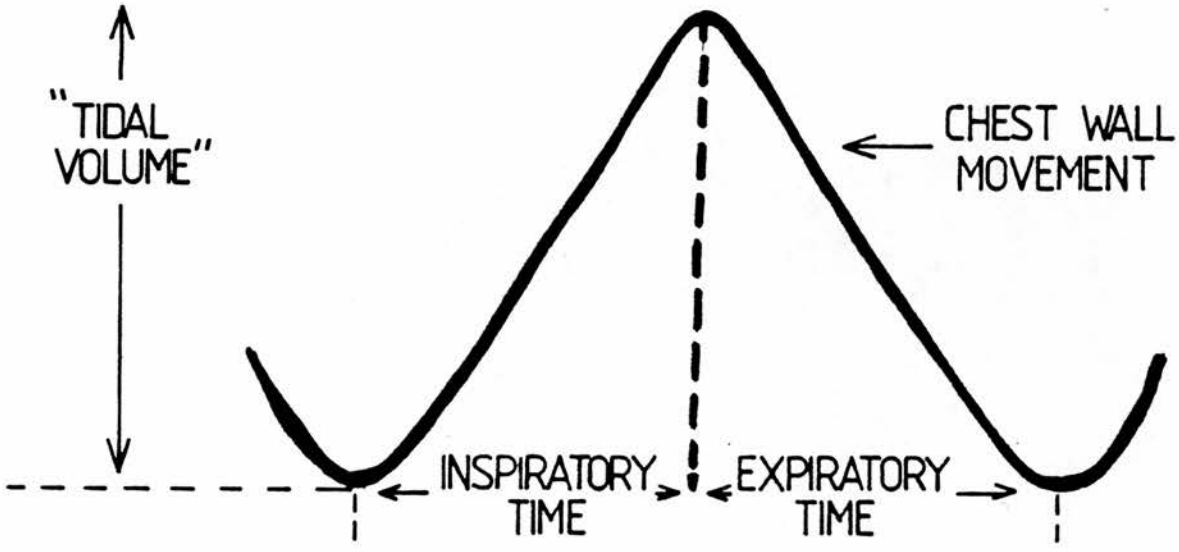

Figure 3 Analysis of a breath.

Evidence suggests that all of these variables can be controlled by various mechanisms such as reflexes (e.g. vagal afferentation) and chemoreceptor stimulation. This interaction of the various mechanisms give rise to a specific breathing cycle. The exact nature of this interaction is not fully understood (Bradley, 1977; Clark and Von Euler, 1972; Von Euler, 1979; Gautier, 1980; Guz and Trenchard, 1971; Paintal, 1970; Renmers, 1976). However, one can regard the breathing cycle as the result of a "driving mechanism" (inspiratory neurons firing) caused by cyclic "timing mechanisms" (Grunstein et al, 1973; Milic-Emili and Grunstein, 1976). Minute ventilation, the product of Vt and f can be broken down into a "driving" and a "timing" component thus (Milic-Emili and Grunstein, 1976):

$$VE = f.Vt = \frac{Vt}{Ttot} = \frac{Vt}{Ttot} \times \frac{Ti}{Ti} = \frac{Vt}{Ti} \times \frac{Ti}{Ttot} \qquad \text{Equation 2}$$

where the mean inspiratory flow (Vt/Ti) is an index of the intensity of the "driving mechanism" and Ti/Ttot represents timing in terms of the fraction of the respiratory cycle occupied by inspiration.

Clark and Von Euler (1972) popularised the concept of studying Vt/Ti relations initially proposed by Barcroft and Margaria, (1932) who suggested that a more detailed analysis of the breathing pattern would provide greater information on respiratory centre drive. They

proposed that minute ventilation should be analysed in terms of "1) the duration of the phases of respiration and 2) upon the rates at which air is driven in and out during the phases". As VE increased, initially Ti remained constant. At a certain threshold (which varies from individual to individual) Ti starts decreasing. In most individuals this occurred at twice resting value of VT. This threshold was held to be the region where inspiration was terminated by bulbopontine mechanisms.

In conscious man breathing during rest at a steady state is irregular. Breath by breath analysis by Priban (1963) has demonstrated that Vt and f are inversely correlated, indicating that VE is relatively constant at a given steady state. This confirmed the studies by Dejours et al (1960). Newsom Daves and Stagg (1975) have shown that a plot of Vt/Ti at rest in normal subjects is a linear function which passes through the origin. This would indicate that inspiratory flow on a breath by breath basis is constant. This data was obtained with a face mask, dead space 140ml, in a supine position. The work by Askanazi et al (1979) agreed that at rest Vt and Ti are linearly related, however, the regression does not pass through the origin, indicating inspiratory flow on a breath by breath basis is not constant but increases with increased Vt.

The ratio Ti/Ttot indicates the relationship between the duration of inspiration and expiration. It

represents a dimensionless number which reflects the fraction of time during which the inspiratory muscles are active (i.e. on duty) and hence can be conveniently termed the inspiratory "duty cycle" (Wyszogrodski et al, 1978). A prolonged Ti/Ttot is thought to predispose to respiratory muscle fatigue (Roussos and Macklem, 1977) and is of equal importance to the tension developed by the muscle as a determinant of diaphragmatic fatigue (Bellamere and Grassino, 1982 (i) and (ii).

These complex mechanisms are being studied and some progress has been made in determination of the movement of the different parts (abdomen - diaphragm and rib cage) of the chest wall (Goldman and Mead 1973; Grassino, 1974) and in a better understanding of the actions of various respiratory muscles (Macklem, 1979). Furthermore, some attempts have been made to quantitate the various transfer functions involved in the translation of inspiratory neural drive into muscle pressure and flow [Siafakas, 1981 (i) and (ii)].

There now exists several methods of non-invasive monitoring of a patients breathing pattern and thus ventilation and respiratory timing. A brief discussion of these will now be considered along with the main apparatus used in this thesis - the Respiratory Inductive Plethysmograph (Cohn et al, 1978).

CHAPTER 2

Methods used to measure breathing patterns without physical connection to the airway

Conventional measurements of tidal volume and minute ventilation have depended upon breathing via a mouthpiece, with the nose occluded by a nose clip through a spirometer or pneumotachograph. It has long been suspected that mouthpiece breathing alters this pattern and several studies have confirmed this (Gilbert et al, 1972; Askanasi et al, 1980; Douglas et al, 1983), demonstrating that breathing on a mouthpiece may cause respiratory frequency to fall and tidal volume to rise. Using a system which is dependent upon physical connection to the airway has other disadvantages which are listed in Table 1. There now exists a number of indirect methods of measuring ventilation and these will now be discussed (Table 2).

1. Observation

Respiratory frequency can be simply measured by observing chest wall motion over a specified period of time. Despite the simplicity of the task inaccurate measurements are frequently made. The average respiratory frequency of subjects at a public gathering who were not aware of being observed was 17 per minute

(Mead, 1960); since breathing through a mouthpiece is associated with a mean frequency of 12 per minute, this corroborates the magnetometer observations that slowing of respiration occurs with mouthpiece breathing (Gilbert et al, 1972). Although counting the number of respirations over a unit of time is simple, it is clearly unsuitable for long term measurement. Furthermore, tidal volume cannot be accurately recorded.

2. Calipers

Calipers can be used to measure static diameters at the extremes of inspiration and expiration. Austin Flint in a textbook published in 1856 described the use of "Sibson's Chest Measurer (1848)" used to record movement of the thorax. This consisted of a horizontal rod which slid on a vertical rod, with dial and index such that changes to 2.5mm could be estimated. An improvement of this was the stethometer produced by Quain (1850). This consisted of a cord attached to an index working over a graduated dial. Increase in chest circumference produced tension on the cord and the extent of respiratory movement was communicated to the dial. However calipers cannot be calibrated to detect dynamic changes in tidal volume.

3. Circumference

The simple tape measure can be used to estimate chest wall circumference but cannot measure tidal

volume. The bellows pneumograph consists of air filled bellows placed over the anterior chest wall and attached by cloth material. Chest expansion stretches the bellows and the change in pressure within the bellows is sensed by a pressure transducer. This is very cumbersome and is impractical. The recording Thoracometer measures circumferential changes of both the rib cage and abdomen by means of a small paper kymograph carried over the sternum. Again this has not found widespread use.

Mercury in silastic strain gauges were used initially to estimate circumferences of limbs for blood flow but when placed round the rib cage and abdomen measure circumferential changes with respiration (Wade, 1954). Changes in the length and width of the enclosed mercury columns alter their electrical resistance. These mercury columns form part of a balanced Wheatstone bridge; changes in circumference are reflected by changes in resistance and imbalance of the bridge.

Bendïxen et al (1964) then employed a single gauge wrapped around the rib cage to monitor respiratory frequency, however, measurement of tidal volume is inaccurate because change in chest circumference is not a linear function of lung volume change (Agostoni et al, 1965). Shapiro and Cohen (1965) recognised this limitation and used the square of the circumference, assuming that circumference squared is proportional to

the enclosed cross sectional area which is directly related to lung volume change. Furthermore to account for the variable contribution of the rib cage and abdomen to tidal volume separate gauges were placed around each compartment and a calibration procedure later known as the isovolume maneouvre, was employed. Volume measured by this technique agreed closely with direct measurement using a pneumotachograph but there was a marked difference with change in body posture.

4. Sampling at the nares

Thermistors or thermocouples placed at the nares sense respiratory frequency and airflow because the temperature of the expired air is warmer than air at room temperature. They are used more as monitors of apnoeas especially in sleep studies (Sackner et al, 1975). Continuous recording of CO_2 from the nares can be obtained by means of the mass spectrometer but this is a rather expensive method.

5. Radiography

The density of the X ray image of the lung fields lessens with increasing lung inflation and vice versa. Photomultiplier tubes can produce an analog recording of the changes in density of lung fields associated with breathing. Also the movement of the diaphragm with respiration can be tracked with a mechanical device from the fluorscopic image to produce a close relationship

between the expiratory reserve volume and diaphragmatic movement (Wade, 1951). Difficulty of correlation, but more importantly the hazards of X ray exposure have curtailed the use of this technique.

6. Canopy with Neck Seal to Spirometer (Spencer et al, 1972).

This consists of a rigid head canopy and neck seal of foam rubber which is ventilated by an air stream which passes to oxygen and carbon dioxide analysers. A spirometer is attached to provide a breath by breath record of lung volume changes. This device is complex and expensive and would be difficult to use in the acute clinical setting.

7. Body Plethysmograph

A barometric method has been proposed for monitoring of ventilation in new born infants (Drorbaugh and Fenn, 1955; Polgar, 1965). The changes in pressure as a subject breathes depend upon tidal volume, chamber temperature and humidity, alveolar temperature and humidity, carbon dioxide exchange in lung tissue and airway resistance. This technique has not achieved wide acceptance due to the complexity of calculating tidal volume and would be difficult to use in the acute adult setting.

Ventilation may be measured from a constant

pressure variable volume plethysmograph, if the neck and head are placed outside the plethysmograph with the torso isolated within the plethysmograph (Johnson and Mead, 1963). Similarly, isolation of the abdominal excursions from those of the rib cage has been attempted by enclosing the lower torso within a hollow cylinder sealed by a rubber membrane to follow the contours of a line just below the costal margin (Bergofsky, 1964). The portion of the tidal volume attributed to diaphragmatic descent can theoretically be measured.

8. Ballistocardiography

The ballistocardiogram can determine the component of tidal volume contributed by displacement of abdominal contents by measuring the linear momentum of breathing and the centre of gravity of the abdominal bulge between expiratory and inspiratory fractions (Josenhans and Wang, 1970).

9. Jerkin Plethysmograph

This consists of a double layer garment filled with air to achieve positive pressure and is placed around the torso (Heaf et al, 1961). Chest movements produce alterations in jerkin pressure which provides a measure of respiration. The positive pressure within the jerkin has a restrictive effect and may reduce functional residual capacity.

10. Optical Mapping

Recently the technique of optical mapping has been described for measuring breathing (Morgan et al, 1984) and has been used in normal and tetraplegic patients (Morgan et al, 1985) in whom there is often paradoxical motion of the rib cage (Moulton and Silver, 1970; Mortola and Sant' Ambrogio, 1978). In this method the subject is photographed from above whilst a line pattern is projected onto his body from either side. The distortion of the line pattern by the surface of the body produces contour lines when viewed from an angle other than that of projection. Because the camera projector relationships are known, the three dimensional coordinates of the body surface can be extracted from the photograph. Some 500-1000 coordinates of the trunk surface are needed to generate adequate cross sections to compute the volume of the parts visible to the camera. Serial photographs are used to measure chest wall motion and respired volume. The computer programme for this technique performs four principal steps.

1) The spatial x y z coordinates of the 500-1000 points on the trunk surface are used to construct a digital image of the surface relative to a horizontal (that is coronal reference plane close to the bed). 2) The position of the costal margin on that surface is identified. 3) A vertical boundary is dropped from that margin to divide the trunk image into rib cage and

abdominal portions. 4) The instant area volumes and a selection of cross sectional (that is transverse) profiles are generated for each portion. The results of partitioning of ventilation in normal supine subjects by optical mapping are similar to those achieved by other methods (Sharp, 1975).

Although this is an ingenious method it is complicated and requires a cooperative immobile subject in the supine position. Whether this could be used in patients in an acute clinical setting has yet to be investigated, but this remains doubtful.

11. Electric Impedance Plethysmography

In this techique bipolar electrodes are placed on the chest wall and impedance over the lungs increases on inspiration and decreases on expiration (Allison et al, 1964). Despite the many improvements in electrode type, placement and circutry (Logic et al, 1967; Cooley and Lorgini, 1968; Weltman and Ukkestad, 1969; Erlebacher et al, 1974) the instrument remains difficult to calibrate for quantitative measurements and there is a marked deterioration in accuracy with change in posture (Grenvik et al, 1972; Ashutosh et al, 1974). It remains a useful monitor of respiratory frequency and can detect apnoeas, but does not provide a quantitative assessment of ventilation.

12. Linear Differential Transducers

In 1967 Konno and Mead measured the contribution of the rib cage and abdomen to tidal volume by means of changes in antero-posterior diameters in standing subjects by means of threads to cores within linear differential transducers. The end of the thread was fixed to the body surface by means of a partially evacuated ping pong ball which was sealed to the skin with clay. Through a system of pulleys and weights, linear motion could be recorded. This system confirmed their theory that the respiratory system could be shown to behave with two degrees of freedom of motion. This technique however required the subject to be immobilised in the upright posture and so was unsatisfactory for long term monitoring.

Magnetometers

Mead and co-workers in 1967 introduced magnetometers which could measure diameters of the rib cage and abdomen during breathing. The magnetometer which is placed on the body surface, generates a magnetic field sensed by another coil placed on the opposite body surface. Alternating current in the exciter coil generates a magnetic field which induces a voltage in the receiver coil. This voltage induced in the receiver coil is inversely proportional to the cube of the distance separating the two coils, and thus is a non-linear device. The distance between coils is considerable (15-35cm) and the amount of coil movement

is small in relation to the distance (0.5cm for resting breathing, 4cm for vital capacity breathing). Thus measurement of tidal volume may be obtained over the short and fairly linear segments of the calibration curve to minimise the error (Sharp, 1975). Recent improvements in electronic circutry have increased the accuracy of measurements (Vellody et al, 1978).

Coils are placed on the anterior and posterior surfaces of the rib cage and abdomen and the signals are electronically added to provide a "sum" signal thus representing tidal volume. The calibration of the magnetometers to obtain volume from the changes in antero posterior diameters has been accomplished in several ways. The Isovolume method has been the most commonly used calibration technique (Mead et al, 1967) and determines the functional relationship of the volume changes of the rib cage and abdominal compartments. The subject displaces air between the rib cage and abdomen with the glottis closed, in such a way that no compression or decompression takes place in either compartment. Unfortunately, this maneouvre requires trained subjects and certainly patients with pulmonary disease would find this impossible to accomplish. Another way to calibrate the magnetometers is for the subject to breathe in and out of a spirometer with predominantly rib cage or abdominal movement and to solve the scaling factors using linear equations in 2 unknowns (Gilbert et al,

1971).

While magnetometers may provide a quantitative measurement of change in thoracic volume during breathing, they have a number of limitations. Their output is known to be a non linear function of volume change (Mead et al, 1967). Also, as the technique measures changes in the antero posterior diameters, relatively small changes in body position alter the diameter being measured, with resulting loss of calibration causing inaccurate volumetric measurements (Ashutosh et al, 1974; Cohn et al 1978). Finally the problem of antero posterior diameter reflecting cross sectional area has to be considered. In normal subjects during tidal breathing the change in antero posterior diameter is the major determinant of change in cross sectional area, but in patients with obstructive lung disease distortion of the rib cage, as reflected by change of lateral diameter, may occur and invalidate the volume calibration obtained from antero posterior diameters alone (Vellody et al, 1978).

TABLE 1

Disadvantages of Direct Ventilatory Monitoring Devices

1. Alteration in Breathing Pattern
   - Decreases Respiratory Rate
   - Increases Tidal Volume
2. Anxiety and Discomfort
3. Reduced patient mobility
4. Difficulty of usage in young children or uncooperative adults.
5. Inability fo monitor respiratory trends in intensive care unit
6. Technical difficulty in using in sleep studies.

TABLE 2

INDIRECT MEASUREMENT OF VENTILATION

1. Direct Observation
2. Calipers
3. Circumference - Tape Measure
   Bellows Pneumograph
   Recording Thoracometer
   Mercury in Silastic Strain Gauge
4. Sampling at the Nares - Thermistor/Thermocouple
   Continuous analyses of CO_2
5. Radiographic - Fluorodensitometry
   - Tracking of Diaphragmatic Motion
6. Canopy with neck seal
7. Body Plethysmograph
8. Ballistocardiograph for abdominal displacement
9. Jerkin Plethysmograph
10. Optical Mapping
11. Electric Impedance Plethysmography
12. Dynamic Diameters - Linear Differential Transducers
    - Magnetometers
13. Respiratory Inductive Plethysmography

CHAPTER 3

Respiratory Inductive Plethysmography

This device is now becoming increasingly used as a method of measuring ventilation without physical connection to the airway. At present there are only two available devices for measuring lung volumes quantitatively, that is, magnetometers as already discussed and the Respiratory Inductive plethysmograph. Similar to most of the methods described that measure ribcage and abdominal motion, magnetometers may be inaccurate, when measuring changes in thoracic gas volume in the presence of increased airway resistance, because of the effect of gas compression and decompression during respiration (Jaeger & Otis, 1964). Furthermore the Respiratory Inductive plethysmograph detects changes in cross sectional areas of rib cage and abdominal compartments rather than diameters, as do magnetometers, and more accurately measures tidal volume in different body positions, over the vital capacity range, as it is less affected by distortions of rib cage or abdominal shape (Cohn et al, 1978).

The original respiratory inductive plethysmograph consisted of insulated wire stitched in a zig zag pattern, of 2cm pitch onto a vest made of elastic material (Milledge & Stott, 1977). The vest enclosed the complete torso from upper chest to pubis and

consisted of eight continuous complete turns of wire. Later Cohn and co workers (1978) modified this device to two separate coils of wire which form the basis of the presently employed system.

Description of the AC/DC coupled Respiratory Inductive plethysmograph

The Respiratory Inductive plethysmograph (Respitrace, Ambulatory Monitoring Inc, White Plains, NY, USA) consists of 2 coils of teflon-insulated wire sewn onto 2 separate elastic bands 10cm in width which are positioned, one around the rib cage at the 2nd-4th intercostal space and the other around the abdomen at the level of the umbilicus, taking care to avoid the lower costal margin (Figure 4). The bands are taped securely to the skin by surgical dressing to prevent slippage, if a prolonged study is anticipated. The coils are connected to a small oscillator module that cycles at frequencies of 300 kHz and puts out frequency modulated signals of approximately 20 kHz. The frequencies of these oscillations are proportional to alterations in the self inductance of the coils due to changes in the volume of the enclosed part as a result of respiration. The oscillator is connected to a demodulator/calibrator such that the signal is isolated with an optocoupler, thereby providing mains isolation of the oscillator module and the subject. The output of

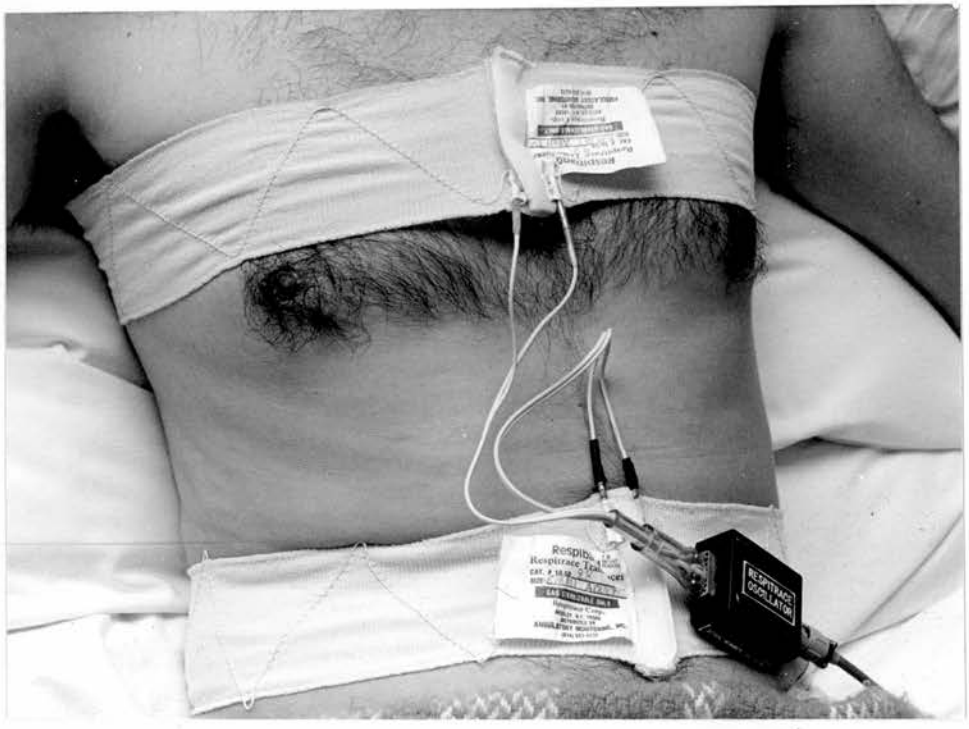

Figure 4 Photograph of the inductive plethysmograph bands.

the optocoupler is then sent to a phase locked loop, which demodulates the signal from the oscillator to provide a DC output signal. The DC-coupling system provides a frequency response that is flat from 0-16 Hz. In addition there is an optional low-pass filter with a time constant of 100 seconds, which may be used in order to restore the signal outputs to a fixed baseline. This latter mode is the AC coupled version. The outputs from the filters go to scaling amplifiers and then to a recording device.

Calibration of the Respitrace

Methods

The accuracy of this equipment for clinical application depends upon the initial calibration and stability of calibration during changes of body position and lung volume. A number of calibration techniques have been proposed. The isovolume angle calibration initially described for magnetometry (Konno & Mead, 1967) requires a special breathing maneouvre that may be difficult to perform by untrained subjects, if not impossible in patients admitted with acute respiratory illness. The method of Stagg and associates (1978) analysed the fractional contributions of rib cage and abdominal excursion of individual breaths during tidal breathing in the supine position but the accuracy of this method has been tested in that body posture only.

A simultaneous equation method (Cohn et al, 1978; Sackner et al, 1980) used 2 body postures to vary the differences in rib cage and abdominal contributions to the tidal volume, but it was sensitive to large errors when only slight differences in the fractional contributions were measured. Latterly, the least squares method has been devised which is thought to be subject to less erros than the simultaneous equation method, when differences in the fractional contribution of rib cage and abdominal excursions in 2 body postures are small (Chadha et al, 1982). These different methods will be briefly reviewed and assessed.

Isovolume Maneouvre

This method is based on the assumption that

1) The respiratory system behaves with 2 degrees of freedom of motion such that the volume (VOL) change at the mouth (open system) is equal to the sum of the volume changes of the rib cage (RC) and abdominal (ABD) compartments:

VOL = RC = ABD

2) With the mouth occluded (closed system) the system has only 1 degree of freedom and any volume change of the rib cage must be equal and opposite to that of the abdomen (Konno & Mead, 1967).

With the mouth occluded and at a constant lung

volume the subject voluntarily shifts volume from rib cage to abdomen and vice versa. This is the isovolume maneouvre. The signals are displayed on a oscilloscope such that the RC signal is the ordinate and the ABD signal is the abscissa. If the signals are scaled correctly, a tracing will produce a line with an angle of 45^{o}. The gain of one or either of the RC or ABD compartments is then raised or lowered to adjust the trace on the graphic display to approximate a 45^{o} angle. The output of the sum of the RC and ABD signal is then recorded against spirometry and the individual gain of the RC and ABD compartments are adjusted equally to render the sum equivalent to the tidal volume recorded by spirometry.

Simultaneous Equation Method (Milledge and Stott, 1977; Cohn et al, 1978; Sackner et al, 1980).

This calibration procedure is based on the assumptions of the isovolume calibration method and on the fact that the distribution of RC and ABD compartments usually varies from one body position to the other; for example ABD excursions predominate in the supine and RC excursions in the standing position (Cohn et al, 1978). Changes in tidal volume recorded from spirometer are recorded along with changes in RC + ABD volume signals while breathing in the supine and standing positions, and the following 2 equations for

the RC and ABD gain factors X and Y are solved thus

$$VOL = X\,(RC) + Y\,(ABD) \quad \text{- Supine}$$

$$VOL' = X\,(RC') + Y\,(ABD') \quad \text{- Standing}$$

where VOL + VOL' are the spirometer volume signal changes during tidal breathing when supine and standing, and RC and RC' and ABD and ABD' are the RC and ABD signals respectively, of the Respiratory Inductive plethysmograph.

The gains are solved as follows:-

$$X = \frac{[(ABD)\,(VOL') - (ABD')\,(VOL)]}{[(RC')\,(ABD) - (RC)\,(ABD')]}$$

$$Y = \frac{[(RC)\,(VOL') - (RC')\,(VOL)]}{[(RC)\,(ABD') - (RC')\,(ABD)]}$$

By multiplying the RC excursion signal by X and the ABD excursion signal by Y, the calibration of the Respiratory Inductive plethysmograph is made equivalent to the spirometer volume. In practice, 20 seconds of the tidal volume excursions are collected. The analogue signals are digitalized at 20 points/sec with a digital computer. These points are measured at the mid - 50% of the inspiratory limb of tidal volume along with corresponding time point values for the RC and ABD tracing. The differences are paired from the supine and standing data collections and the gains are computed for each pair and then averaged yielding a mean. This

technique has been used to successfully calibrate the Respiratory Inductive plethysmograph in adults (Sackner et al, 1980), adolescents (Tabachnik et al, 1981 (i) and (ii) and infants (Duffty et al, 1981).

Method of Stagg and associates

This method was introduced to calibrate magnetometers with the aid of a computer, but without requiring special respiratory maneouvres (Stagg et al, 1978). This technique is based on the assumption that the normal variation occurring during spontaneous breathing contains sufficient information to describe the relationship between the rib cage and abdominal components and volume measured at the mouth. During initial inspiration, volume change is produced predominantly by abdominal displacement. The contribution of the rib cage progressively increases so that at the end of inspiration, volume change is predominantly due to rib cage motion. Using a computer to sample the signals at 25 points per second will field 30 or 40 observations on the relative contribution of the rib cage and abdomen to each single breath. Thus, a single breath will produce a matrix of 30 to 40 linear equations in two unknowns which can be solved by a computer, for the best-fit estimates and by repeating this procedure for several breaths the variance can be reduced further. Accuracy of this calibration method is

dependent on the subject maintaining the same body posture as deviation from spirometry is very large with change in body posture.

Least Squares Method (Chadha et al, 1982)

This method is described by Chadha and colleagues and has the same assumptions as the simultaneous equation method and is based on using the RC and ABD displacements and the spirometer volumes:

$$\frac{RC}{SP} + \frac{ABD}{SP} = 1 \quad \text{where SP = spirometer volume}$$

It reflects the proportionality of the sum equaling a constant value as in the isovolume calibration method and is calculated with the spirometer as a reference as in the simultaneous equation method. When the correct ratio of RC/SP on the Y axis and ABD/SP on the X axis are plotted on a linear graph, the slope obtained is a line with the intercepts of 1.0 on both axes. If the inspired breath is distributed solely to the rib cage, the RC/SP ratio should be 1.0 and conversely, if the inspired breath is distributed to the abdominal compartment the ABD/SP ratio should be 1.0.

Data is collected for the spirometer, RC and ABD signals in 2 positions in the same manner as in the simultaneous equation method. Analyses of each recorded breath yields a delta value (Vmax - Vmin). Vmax is defined as the apex of the spirometer signal and Vmin is the maximum depression occurring one-half cycle later. Delta values for the 3 signals are measured for each

breath in each of the 2 positions and the RC/SP and ABD/SP ratios calculated. These values for each breath are plotted as coordinate pairs with the RC/SP as the Y value and the ABD/SP as the X value. The minimal error line through these points can be derived with a least squares fit calculated by a digital computer. The rib cage scaling factor is then the reciprocal of the Y intercept, and the abdominal scaling factor the reciprocal of the X intercept.

Although the least squares and simultaneous equation method are mathematically equivalent, there are differences in practical application between the two methods. The least squares method is thought to be more accurate in humans than the simultaneous equation method originally described. The increased reliability of the least squares method is based on the fact that wide differences in the volume distribution of rib cage and abdominal contributions are not required for a minimum error calibration, whereas the previous simultaneous equation technique was sensitive to error when only slight changes in volume distribution were present (Chadha et al, 1982). Furthermore, the graphic solution of gains in the least squares method is easier and does not require a digital computer.

In a study carried out by Chadha et al (1982) they compared the calibration of simultaneous equation, the least squares and the method described by Stagg et al (1978) against spirometry. They found that the least

squares method gave 89% of Respiratory Inductive plethysmography values to within ± 10% of simultaneous spirometry. The simultaneous equation method gave 91% within ± 10% of spirometer values. However, the method of Stagg et al (1978) gave only 66% of values within 10%. Similar figures were found by Bellia et al (1984) who compared the simultaneous equation method and least squares method over a total of three hours. They found the mean error for the whole sample to be low: 7.6% for the simultaneous equation method and 7.3% for the least squares method, although they did note a wide variability of results.

However, this was further studied by Zimmerman and colleagues (1983). They determined tidal volume derived from Respiratory inductive plethysmograph signals by the method described by Sackner et al (1980) and by the isovolume technique (Konno & Mead, 1967) and compared them with independently measured spirometric volume changes. Errors in tidal volume as measured by the isovolume technique averaged 6%. When the change in posture technique (Simultaneous equation method) was used to assess the calibration factors, they found that estimates of tidal volume showed a mean deviation of 9-18% in the upright, semirecumbent and supine postures. When using the semirecumbent and supine postures to determine the calibration factors by the change in posture technique, the error in estimates of tidal

volume ranged from 13 to 23%. Zimmerman et al postulate that under conditions of expected clinical use the accuracy appears to be approximately 15% for the change in posture (simultaneous equation method) and approximately 7% using the isovolume calibration in a given posture. However, these latter investigators did not adhere to the calibration procedure as reported by Chadha et al (1982) which recommends that if the initial validation shows a greater than 10% deviation from spirometry, the ribcage and/or abdominal bands should be repositioned and a new set of calibration factors obtained until this deviation is less than 10%. Zimmerman and co workers (1983) maintained the coils in a predetermined position even though they demonstrated large deviations from spirometry in their initial validation.

More recently Loveridge et al (1983) have introduced a single position calibration of the Respiratory Inductive plethysmograph. This calibration technique is similar to that previously described by Stagg et al (1978) with magnetometers. They found good correlation of this method with values obtained from a pneumotachograph, and subjects were able to breath spontaneously and remain in one position making the procedure more applicable to more seriously ill patients than previous calibration procedures have been.

Similarly Hudgel et al (1984) carried out a modified change in posture calibration technique (Tobin

et al, 1983) on patients with chronic obstructive airways disease. They assessed tidal volume accuracy at different respiratory frequencies in different body positions with different thoracic and abdominal contributions to breathing over a four hour time span. The mean error of tidal volume estimation was 7.6% for all body positions studied and the tidal volume accuracy was unchanged after four hours, and unchanged with changes in the thoracic and abdominal contributions to tidal volume. They also compared respiratory timing and found mean errors for inspiratory and expiratory times were 3.3 and 2.0% respectively.

In weak or ill patients the pattern of respiratory efforts may vary considerably with their clinical state. Such patients present the greatest potential problem in monitoring ventilation. They would certainly be unable to perform isovolume maneouvres and would be too ill to collaborate with the calibration technique of spirometry in two postures. Clearly, the use of complex calibration techniques is curtailed in the acute clinical setting. Thus to study patients breathing patterns who have been admitted with acute respiratory illness, a simple calibration technique which is patient acceptable has been devised. This technique would have to be, above all, safe, cause the patient little distress if any and would allow the patient to remain as comfortable as possible throughout any proposed study.

The relative gains of the chest and abdominal movements were thus fixed arbitrarily at unity and the sum of these two signals calibrated when the patient gently inflated a 600ml plastic bag. This calibration procedure assumed no change in the relative contribution of movements of the chest and abdomen. This assumption was verified in the preliminary study of 13 patients with acute severe asthma and 4 patients with an exacerbation of chronic bronchitis and emphysema (Table 3), where there was no change in the ratio of movement of the rib cage to abdomen after bronchodilation (for asthmatics), mean rib to abdomen amplitude ratio pre-bronchodilator 0.7 SEM 0.1, post-bronchodilator 0.7 ± 0.2 arbitrary units. For patients with chronic bronchitis and emphysema mean rib abdomen amplitude ratio pre-bronchodilator 0.6 ± 0.1, post-bronchodilator 0.6 ± 0.7 arbitrary units.

In an effort to determine whether an improvement on this technique could be demonstrated, the effect of trying to change the gain ratios of rib to abdomen was studied. One normal subject (PKW) completed two ten minute periods of spontaneous breathing into a Bell spirometer separated by 25 minutes. During these periods the sum, abdomen and rib signals from the inductive plethysmograph and the Bell spirometer were sampled 50 times per second, and the samples stored on a floppy disc on a mini-computer (MINC 11 computer). The subject remained supine for the whole of the study.

In the analysis successive minute periods were taken from the two blocks of data and a multiple regression analysis performed of the spirometer level on the ribcage and abdomen signals. From this the ratio of the rib cage and abdomen calibration factors was calculated for each minute. The results of the analysis as shown in Table 4 and it can be seen that the required ratio varied between 1.4 and 0.7, a variation of 2:1. Next an analysis of each breath of the two periods was carried out, calculating the regression onto the spirometer signal of

a) the Respiratory Inductive plethysmograph sum signal
b) the sum of the rib and abdomen signals
c) the sum of the rib and abdomen sealed in accordance with some chosen ratio.

From this data it was found that there is a close correlation of the bell with each of these variables in any one breath, but that the regression coefficients varies from breath to breath. The purpose of changing the gain ratios was to reduce this variability. Thus the above analysis was then re-run with each of the gain ratios shown in Table 4 and calculation of the coefficient of variation of the breath by breath regression coefficients carried out. However from this, by chosing the gain ratios carefully there was a

reduction in the coefficient of variation to 8.2%, compared with 8.6% if it was fixed arbitrarily at unity. The corresponding figures for the second run were 7.7%, compared to 8.7%.

Thus, the conclusion that can be drawn from this is that there is no significant improvement if the gains of rib cage and abdomen are changed and that tidal volume can be measured to within 8% over a period of 30 minutes. This is in keeping with other estimates of tidal volume (Chadha et al, 1982; Bellia et al, 1983, Hudgel et al, 1984), carried out with different calibration procedures.

All of the values for the comparison for timing events of respiration (frequency, time of each breath and inspiratory and expiratory time) for the inductive plethysmograph have been within 3% of the values obtained by spirometry (Sackner et al, 1980; Hudgel et al, 1984).

Computer designation of breath

Data was collected on-line at the bed side by a MINC (PDP 11/05) mini computer, Digital Equipment Corporation. The computer programme was MACRO-11 run under the RT-11 operating system. The inductive plethysmograph signal processing was carried out as follows (Fig 5).

All the various analogue signals input to the

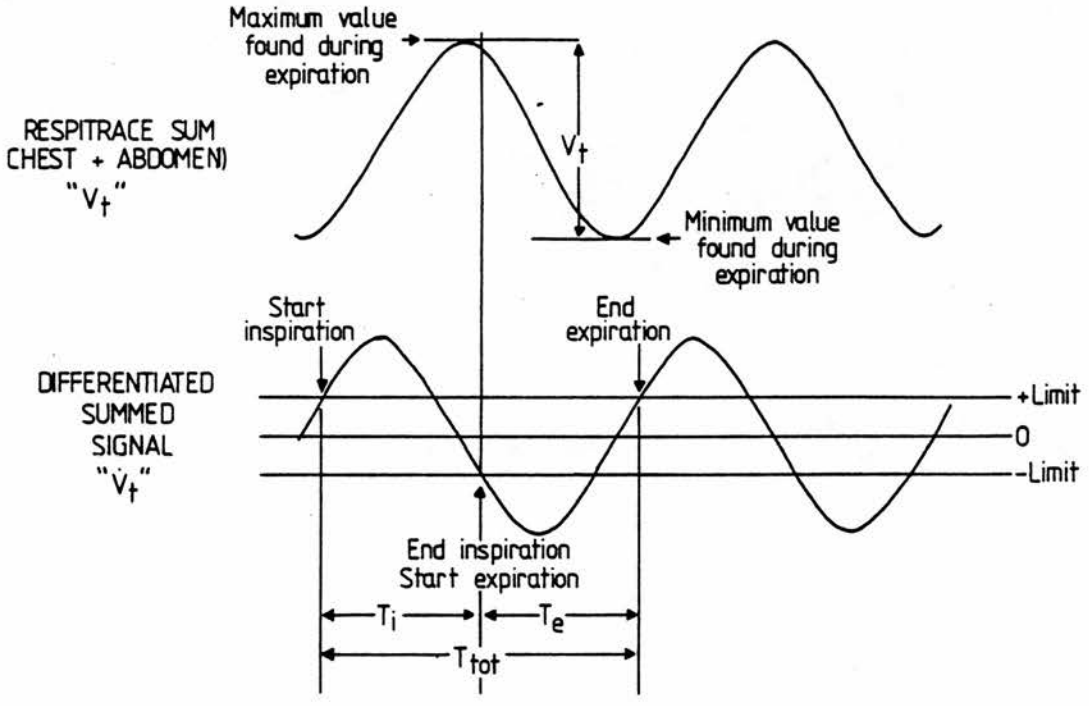

Figure 5 Signal processing.

computer are sampled by the analogue to digital converter (ADC) every 20 milliseconds. A "new" signal is constructed from the inductive plethysmograph signal by differentiating it; in detail by subtracting from the current value the value obtained 8 samples ago. All the breath phases are derived from the new signal, which will be referred to as VDIFF.

At any instant all the values VDIFF over the previous minute are stored in the computer. These are used to compute two sets of limits referred to here as the inner and outer limits. These are respectively 0.5 and 3.0 standard deviations on either side of the mean of the last minutes worth of VDIFF.

The inner limits are used to identify the breath phases. While the programme is seeking for the end of inspiration, it waits for VDIFF to go below the lower of the inner limits (see Fig 5). When this point is reached, the time is noted, new limits are computed, and the programme starts to search for the end of expiration. In this phase the programme waits until VDIFF rises above the upper inner limit (Fig 5). At this point it stores the time of end expiration, sends the result of last breath to the backing store and the display, re-initialises itself for the next breath, and starts searching once more for the end of inspiration.

The outer limits referred to above are used to prevent the inner limits from changing too quickly. If

a VDIFF sample is outwith these limits it does not contribute to the mean and standard deviation calculated and hence does not affect the updated limit.

While the breath phase programme is going on the programme is also maintaining the maximum and minimum it finds in each of the inductive coils and the average ear oxygen saturation. These form the "results for the last breath" stored at each end expiration, and it is the stores holding these results that are re-initialised after their contents have been written away.

Ear Oxygen Saturation

With the recent advances in technology, not only is it possible to record ventilation and timing by surface techniques, but recording of oxygen saturation by means of ear oximetry can be carried out. Previous instruments had problems with instability and insensitivity (Saunders et al, 1976; Chaudhary et al, 1978) but these have been overcome. The accuracy and sensitivity to carboxyhaemoglobin of the Hewlett-Packard 47201A ear oximeter was studied by Douglas et al (1979) who found that this instrument could measure $Sa0_2$ in the range 65-100% with an accuracy of $\pm$ 4% (95% confidence limits). Thus ear oximetry offers an attractive non-invasive method for monitoring arterial oxygenation which will allow continual recording of oxygenation even during sleep (Flick et al, 1977; Douglas et al, 1979).

TABLE 3

RIBCAGE TO ABDOMEN RATIO BEFORE AND AFTER BRONCHODILATATION

Patient ASTHMA	Age(Yrs)	Sex	PEFR on Admission ℓ/min	PEFR after Admission ℓ/min	Breaths over 15 Minutes	Ratio before Bronchodilatation	Ratio after Bronchodilatation
CK	22	M	160	250	391	0.26	0.41
EM	29	F	<60	130	343	1.27	1.58
AT	21	F	280	330	257	0.66	0.71
CM	24	M	200	250	213	1.28	1.18
AS	23	F	260	350	183	0.73	0.78
CM	17	F	165	215	246	0.43	0.44
RS	17	M	260	285	223	0.55	0.25
CM	21	F	80	120	386	0.95	0.93
JB	40	F	160	260	297	1.16	1.21
VB	38	F	300	370	286	0.69	0.58
GS	18	F	200	250	327	0.25	0.25
DY	49	F	200	360	257	1.04	0.83
RC	54	M	190	260	276	0.46	0.64
						NS (paired t test)	

TABLE 3 (contd)

Patient	Age(Yrs)	Sex	PEFR on Admission ℓ/min	PEFR after Admission ℓ/min	Breaths over 15 minutes	Ratio before Bronchodilatation	Ratio after Bronchodilatation
CHRONIC BRONCHITIS AND EMPHYSEMA							
RB	69	M	140	160	292	0.55	0.60
JF	68	M	190	190	277	0.61	0.55
RC	70	M	230	250	258	0.92	0.76
GD	73	M	140	170	343	0.32	0.38
				-		NS	

TABLE 4

RATIO OF RIBCAGE TO ABDOMEN CALIBRATION FACTORS FOR EACH MINUTE

Run 1	Run 2
1.374	1.299
1.223	1.211
1.229	1.141
1.095	1.213
1.099	1.108
0.992	1.070
0.972	1.136
0.921	1.114
0.899	1.061
0.846	1.081
0.834	1.065
0.789	1.018
0.709	0.957

CHAPTER 4

The effect of bronchodilatation on breathing patterns in asthma and chronic bronchitis and emphysema

The response of bronchodilator drugs in respiratory disease is usually assessed by forced expiratory flow rates. However, measurement of spontaneous ventilation is rare in acute asthma or chronic bronchitis and emphysema as such patients will not tolerate the equipment required for such measurements. As previously discussed, these methods are known to alter breathing pattern (Gilbert et al, 1972). However, newer surface techniques have recently been applied to the acute clinical setting (Duffty et al, 1981; Tobin et al, 1983; Tobin et al, 1984). By using the Respiratory Inductive plethysmograph and ear oximeter it is now possible to examine the effect of alteration of airway calibre on breathing pattern in patients admitted with airways obstruction. Furthermore, it may be possible to correlate a change in breathing pattern with change in airway calibre. Two groups of patients were studied. The first group consisted of patients admitted with variable airways obstruction, that is acute asthma. The second group were ten patients with fixed airways obstruction, namely chronic bronchitis and emphysema. Both groups received standard bronchodilator therapy and

the effect on breathing pattern and oxygen saturation recorded.

Methods

Ten patients with acute spontaneous asthma were studied, (Table 5) each having a peak flow rate of less than two thirds of their best out patient value (mean peak flow rate on admission 193, range, <60-400l/min). All asthmatics had been shown to increase their FEV_1 by more than 20% with inhaled beta-2 agonists when clinically well. The 10 patients admitted with an exacerbation of chronic bronchitis and emphysema were known to have irreversible airways obstruction and had an average peak expiratory flow rate on admission of 142l/min (range 100-230l/min). None of the asthmatic patients were smokers, but all 10 patients with chronic bronchitis were smokers. All studies started within 18 hours of admission, with an average six hours between starting the study and admission, and none started within four hours of nebulised or intravenous broncho-dilator therapy. Six of the ten asthmatic patients received one bolus of aminophylline on admission but none were receiving continuous theophylline infusion. All asthmatic patients received hydrocortisone 200mgs IV on admission and 40mgs per day of oral prednisolone thereafter. All asthmatic patients received supplementary oxygen of at least four litres/min, the patients with chronic obstructive airways disease received controlled oxygen therapy from 1-2 litres/min

depending on arterial blood estimations.

Treatment

All 10 asthmatic patients received terbutaline (4mgs) made up with 0.5ml normal saline to 0.9ml in total. All patients with chronic bronchitis and emphysema received a combination of terbutaline (4mg) and ipratropium bromide (100 micrograms) in 0.5 ml normal saline. All solutions were nebulised to dryness in a Wright's nebuliser with 4l/min oxygen.

Procedure

Peak expiratory flow rates were measured at the start of the study and at half hourly intervals for one and a half hours after nebulisation. Breathing patterns were measured by an inductive plethysmograph with one band taped securely at the level of the 2nd-4th intercostal space anteriorly and the other at the level of the umbilicus. As these patients were acutely ill, they could not tolerate the complex maneouvres required for calibration, such as the two posture, isovolume or spirometric technique. The Respiratory Inductive plethysmograph was calibrated as described on Page 52. The inductive plethysmograph summed signal, with gains fixed arbitrarily at unity, was calibrated when the patient gently inflated a 600ml plastic bag. As previously discussed this calibration assumes no change in the relative contribution of the chest and abdomen,

an assumption verified in a preliminary study of 13 patients with acute asthma and four patients with an exacerbation of chronic bronchitis and emphysema, where there was no change in the ratio of movement of the rib cage to abdomen after bronchodilatation (see Chapter 3). Oxygen saturation was measured by the Hewlett Packard 47201A ear oximeter (Douglas et al, 1979). The studies were carried out in the acute clinical setting, by the bedside and breathing pattern and oxygen saturation recorded on-line on a bedside minicomputer (Figure 6). After the equipment was attached and the patient had settled, control data was recorded for 15 mins and then the patient received nebuliser therapy. Breathing patterns and oxygen saturation were continuously monitored for a further 90 minutes. Data was analysed off-line by the same computer. The data reported compares control data with that obtained between 75 and 90 minutes after nebulisation, unless otherwise stated. Values are given as mean and standard error and the significance of differences were determined by paired t test (Snedecor and Cochrane, 1980). All patients gave informed consent to the study which had the approval of the Hospital Ethical Committee.

Results

All 10 asthmatic patients increased their peak flow rate following inhaled bronchodilator therapy, their peak expiratory flow rate rising from a mean of 193±34 to 291±32 l/min (Table 6, Fig 7). Amplitude of thoraco

Figure 6 Clinical monitoring of a patient at the bedside.

abdominal movement (Vt) fell from 0.43±0.09 to 0.34±0.07 ($p<0.01$, Fig 8, 11), inspiratory drive (mean inspiratory flow, Vt/Ti, where Ti is duration of inspiration), also fell from 18.6±2.9 to 13.8±2.3 units/min ($p<0.01$, Fig 7,9). There was a fall in ventilation (Vt/Ttot where Ttot is breath period) from 8.4±1.5 to 6.5±1.1 units/min ($p<0.01$, Fig 8,10). The respiratory duty cycle (Ti/Ttot) rose from 37.5±1.2 to 39.4±1.2 but this was not significant. Furthermore, there were no significant changes in expiratory time, inspiratory time or breath period. As the asthmatic patients were on supplementary oxygen, oxygen saturation did not change (mean 95±0.7 to 94.6±0.8, not significant).

In contrast, there was no increase in peak flow rate following bronchodilators in the ten patients with chronic obstructive airways disease (Table 7). There was no change in inspiratory drive (Fig 12), tidal volume and ventilation, nor in respiratory timing in these patients. These patients were receiving controlled oxygen therapy and their oxygen saturation did not change significantly following bronchodilators, (mean $Sa0_2$ before bronchodilators 92.8±1.1, 91.3±1.8% after bronchodilators).

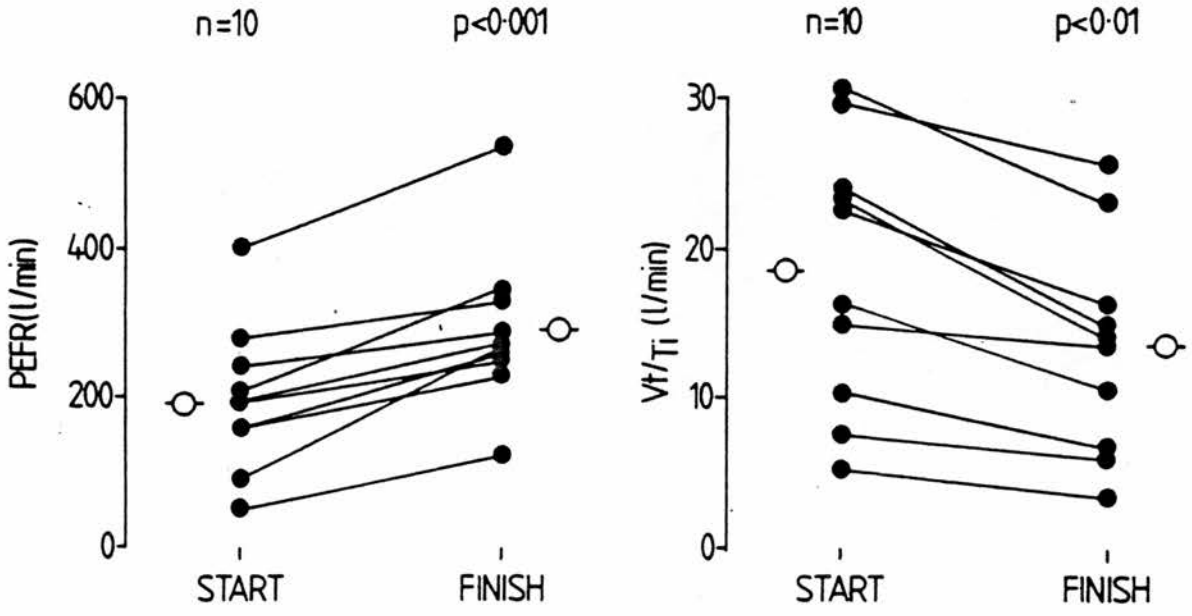

Figure 7 Effects of bronchodilator on peak expiratory flow rate and inspiratory drive in acute asthma.
PEFR pre B2 agonist - 193±4L/min.
PEFR post B2 agonist - 291±2L/min.

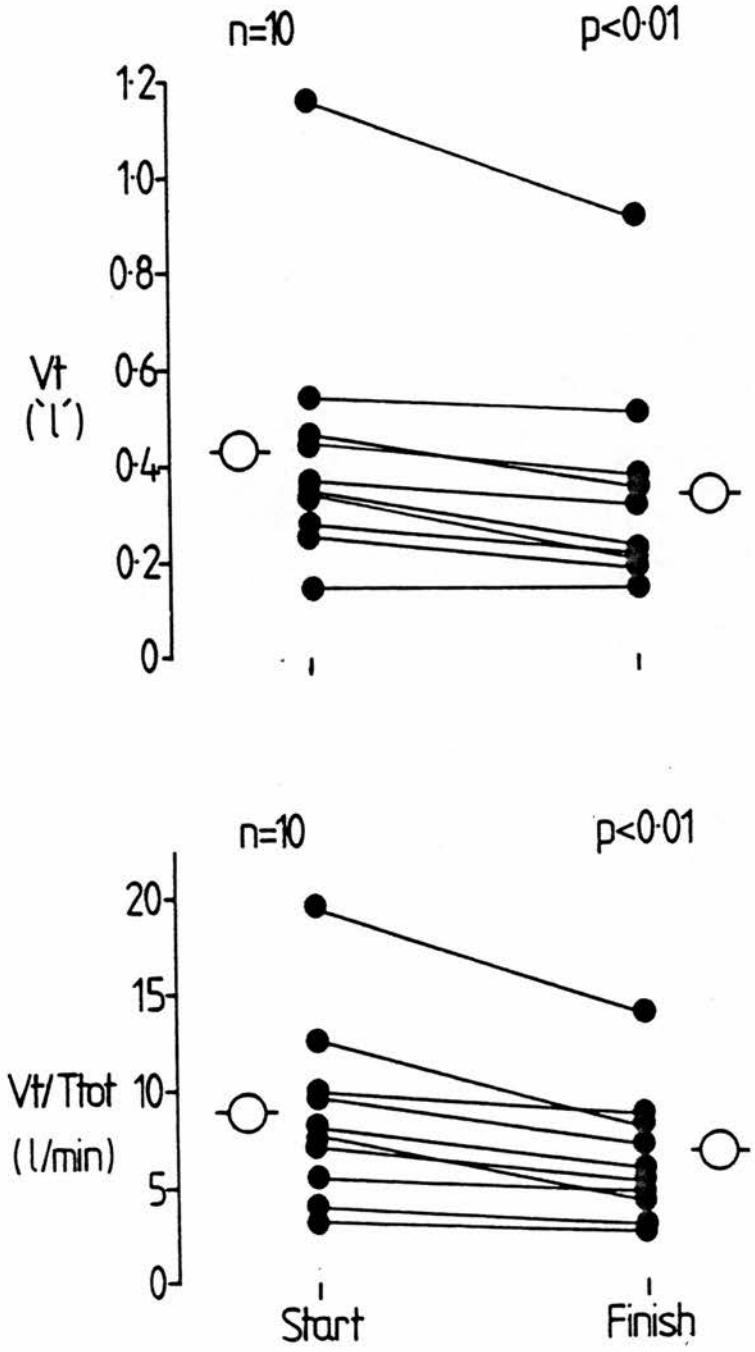

Figure 8 Fall in tidal volume (Vt) and ventilation (Vt/Ttot) with bronchodilatation in acute asthma.

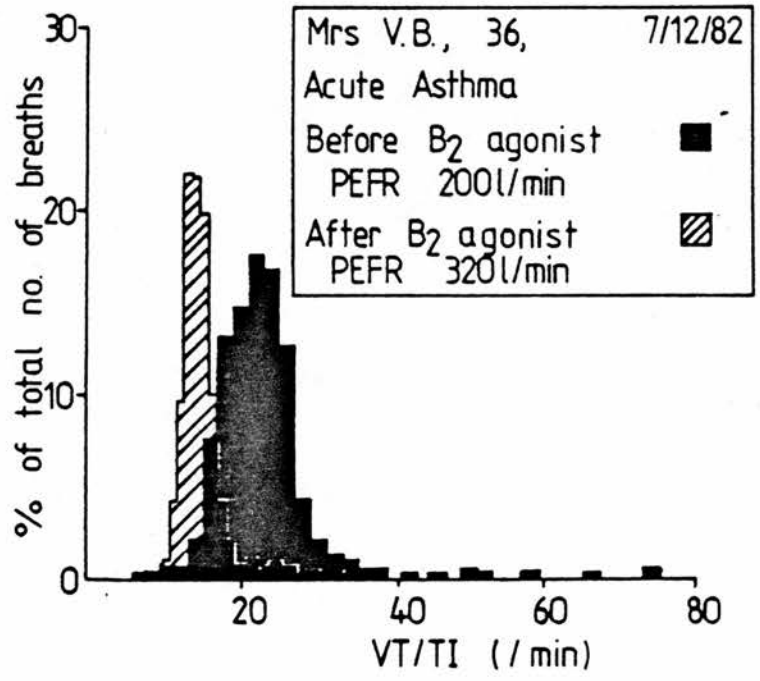

Figure 9 Fall in inspiratory drive (Vt/Ti) in acute asthma after bronchodilator in one patient.

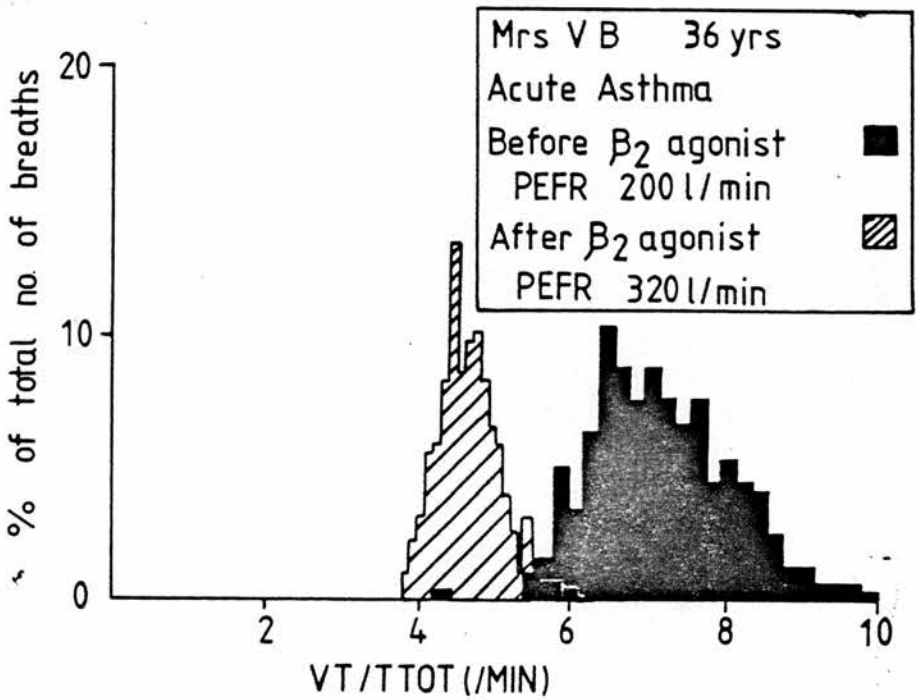

Figure 10 Change in ventilation (Vt/Ttot) after bronchodilator in acute asthma in one patient.

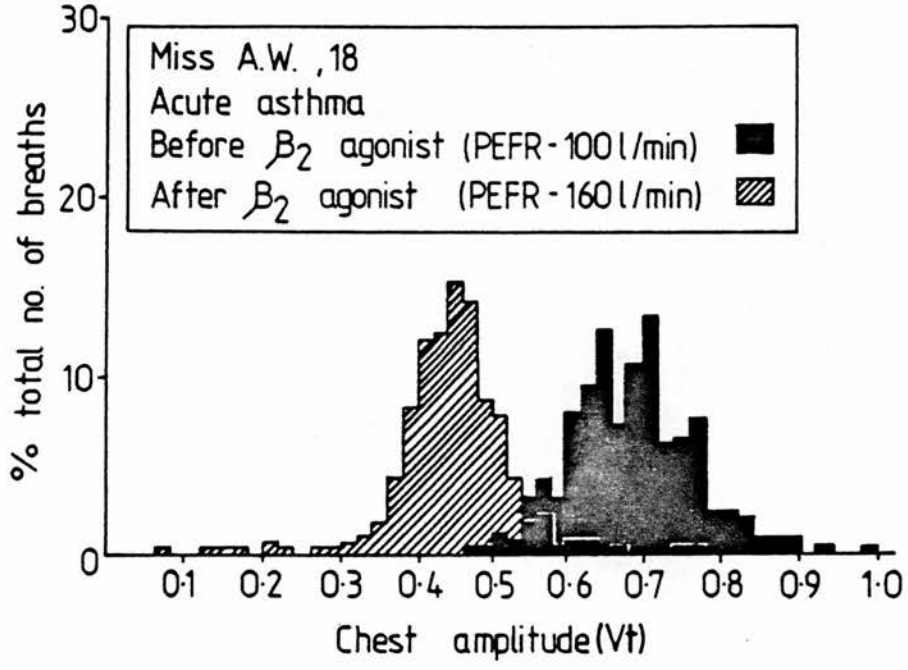

Figure 11 Fall in tidal volume (Vt) after bronchodilator in acute asthma.

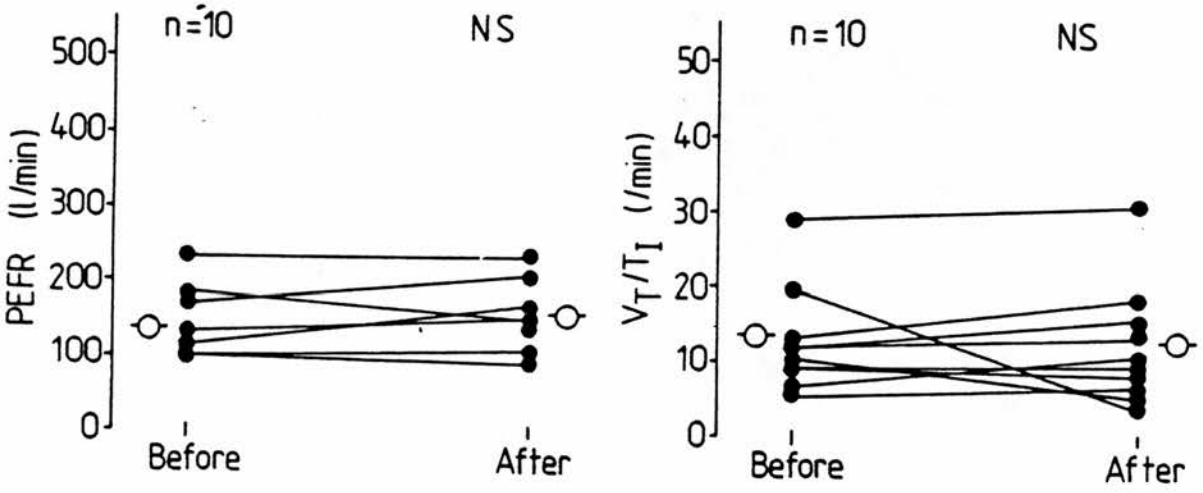

Figure 12 Effect of bronchodilator on peak expiratory flow rate and inspiratory drive (Vt/Ti) in patients with chronic obstructive airways disease.
PEFR pre B2 agonist - 142±15L/min
PEFR post B2 agonist - 159±14L/min.

Discussion

Clinical improvement following bronchodilators in acute asthma was associated with a reduction in tidal volume and a parallel decrease in minute ventilation and inspiratory drive, whereas no such changes occurred within 90 minutes of bronchodilator therapy in patients with an acute exacerbation of chronic bronchitis and emphysema.

Ventilation is increased in patients with an acute attack of asthma, when, as in the present study $PaCO_2$ (4.9 ± 0.2kPa) is usually low when patients are breathing spontaneously (Tai and Read, 1967; McFadden and Lyons, 1968; Rees et al, 1968; Miyamoto et al, 1979). The low Pco_2 is usually accompanied by respiratory alkalosis, in adults, however, respiratory acidosis in children has been found (Simons et al, 1977; Simpson et al, 1968). As previously discussed actual measurements of ventilation are rare in severe asthma and this is where the application of surface techniques such as the Respiratory Inductive plethysmograph may be of benefit.

In unsedated dogs (Cotton et al, 1977) and monkeys (Pare et al, 1976) antigen challenge induces both bronchoconstriction and rapid shallow breathing. In an attack of clinical asthma in man, there is a characteristic increase in functional residual capacity (FRC) (McFadden and Lyons, 1969) and this increases the

stiffness of the lungs in the tidal volume range at this high FRC. This coupled with the increased airways resistance and rapid breathing, must increase the metabolic cost of breathing, although this has not been directly measured in the acute attack of asthma for the reasons given above. The low $PaCO_2$ when combined with the increase in CO_2 production, must therefore imply that alveolar ventilation is increased.

Despite this hyperventilation, arterial hypoxaemia is usually encountered in the asthmatic attack, thought to be due largely from an increase in the variation of the distribution of ventilation to perfusion ratios (V/Q) (Flenley and Warren, 1985). This has been shown in asymptomatic asthma (Wagner et al, 1978) but as such measurements are only valid in a steady state they have not been used to confirm the ventilation perfusion abnormalities in the acute clinical attack of asthma. It is thought that the hypoxic ventilatory drive alone was unlikely to achieve this degree of hyperventilation (Rudolf et al, 1980; Karetzky, 1975). Correction of this hypoxaemia in the asthmatic by oxygen therapy does not restore $Pa0_2$ to normal values (Kassabian et al, 1982), indicating that other factor or factors must be stimulating ventilation.

The ventilatory response to CO_2 is depressed in some (Zakon et al, 1976) but not all asthmatics (Hutchison and Olinsky, 1981). The wide variability in the CO_2 response in normal subjects (Rebuck and Read,

1971; Saunders et al, 1976) also makes interpretation of such measurements difficult. However in the study carried out by Rebuck and Read (1971) 16 out of 19 asthmatics studied, the ventilatory response to CO_2 improved over several days as conventional treatment improved their FEV_1 from the initial airways obstruction. In contrast however, the central respiratory drive (as measured by the mouth occlusion pressure, P 0.1, Whitelaw et al, 1975) was higher for any given Pco_2 during carbon dioxide rebreathing in asthmatics as compared to normal subjects, implying that the central respiratory drive from carbon dioxide was increased in asthma (Zakon et al, 1976), whereas the ventilatory response to carbon dioxide in the same subjects was reduced. This increase in P 0.1 in asthma has been confirmed by Kelsen and co-workers (1979) but in their studies the ventilatory response to CO_2 was normal in asthma. Furthermore, the same authors also found that the response of the central drive (P 0.1) to external flow resistive loading during carbon dioxide rebreathing was increased in asthma and they attributed this effect to stimulation of sensory receptors in the airways (Kelsen et al, 1979). P 0.1 was also increased during spontaneous breathing at rest in moderately severe asthmatics, but there was a slight fall in the mean P 0.1 when oxygen therapy was given to raise the $Pa0_2$, although the $PaCO_2$ still remained low (Kasabian et

al, 1982). Furthermore, the same authors also found that the hypoxic drive to breathing was normal in asthmatics, as assessed by ventilatory responses, and this again has been confirmed in some asthmatic children, (Morrill et al, 1981) but not in others (Smith and Hudgel, 1980).

There is strong experimental evidence that the increased ventilation in acute asthma may be mediated through the vagus. In 4 unsedated dogs during treadmill exercise (Cotton et al, 1977) inhalation of ascaris suum antigen aerosol consistently increased ventilation by increasing rate, despite a fall in tidal volume. This only occurred if the vagi were functionally intact. However, when the vagi (exterorised at a previous surgical procedure) were cooled to inhibit conduction, similar antigen challenge no longer influenced either ventilation, breathing rate or tidal volume, however, pulmonary resistance to airflow still increased, as it did before cooling the vagi (Cotton et al, 1977).

Increased respiratory centre drive as reflected by elevations of ventilation and inspiratory drive and mouth occlusion pressure (P 0.1) have been observed during acute bouts of bronchospasm in asthmatic patients (Kassabian et al, 1982; Guz, 1977). Furthermore, Tobin et al (1984) by using the Respiratory Inductive plethysmograph have shown increased inspiratory drive (Vt/Ti) in symptomatic asthmatics (where FEV_1 was 61% predicted normal). Frequency (f) was normal but tidal

volume was significantly elevated thus leading to an increased ventilation. These findings are confirmed in this study.

As peak expiratory flow rate rose indicating bronchodilatation, the amplitude of thoraco abdominal movement (Vt), inspiratory drive and minute ventilation fell. Thus it is postulated that these changes have occurred via afferent information travelling in the vagus nerves. The increased ventilation in acute asthma is related to bronchoconstriction, and ventilation falls with bronchodilatation.

In this particular study there was concern that the fall in tidal volume might have been an artefactual result of the inductance plethysmograph caused by a reduction in functional residual capacity as the asthmatic patients responded to treatment. It is known that the FRC is considerably increased in asthma (McFadden and Lyons, 1969). Therefore, tidal volume, as measured by the respiratory inductive plethysmograph and spirometry was recorded for over 30 breaths in nine normal subjects (6 males and 3 females) at normal functional residual capacity and at one litre above normal functional residual capacity. There was no difference in the ratio of the inductive plethysmograph derived volume to spirometer volume at the different FRCs (normal FRC - inductive plethysmograph to spirometer ratio 1, FRC + 1 litre - inductive

plethysmograph to spirometer ratio 0.89±0.09; P > 0.1, normalised data). Thus, the difference in ventilation observed in these asthmatic patients as bronchodilatation occurred did not result from a fall in functional residual capacity alone.

Unlike the asthmatic patients, patients with chronic bronchitis and emphysema showed no change in peak expiratory flow rates, nor breathing patterns. Measurements of P 0.1 in patients with chronic obstructive airways disease indicate an increase in respiratory central drive (Aubier et al, 1980; Sorli et al, 1978; Bradley et al, 1979). However, this finding has not been confirmed by all investigators (Gleb et al, 1977). Gleb and co-workers postulate that acute airway obstruction is associated with increased drive as measured by P 0.1 but this may become reduced with chronic obstruction. Tobin et al (1983) looked at 28 patients with chronic obstructive airways disease using an inductive plethysmograph and found that they had breathing patterns similar to asthmatic patients. These patients had moderate elevations of f and Vt and thus minute ventilation was elevated above normal. Similarly, inspiratory drive (Vt/Ti) was markedly elevated above the normal value of 250±58 ml/sec (mean of control data from normal subjects) [(Tobin et al, 1983 (ii)] to almost twice normal [(Tobin et al, 1983 (i)].

In the study carried out for this thesis patients

with acute exacerbations of chronic obstructive airways disease showed no objective change in their clinical condition, that is no change in peak expiratory flow rate could be demonstrated. Although inspiratory drive, as measured by either P 0.1 (Aubier et al, 1980) or Vt/Ti by plethysmography [(Tobin et al, 1983 (i)] may be raised, conventional therapy did not seem to affect this in the chronic bronchitic.

Furthermore, no significant changes in respiratory timing in either the asthmatic group or patients with chronic bronchitis and emphysema were discovered. However, it must be remembered that these patients were studied on average six hours after admission, and thus this does not exclude earlier change in respiratory timing.

TABLE 5

PATIENT DATA

ASTHMA

Patient	Age (yrs)	Sex	PEFR on adm. ℓ/min	pa02 (on admiss kPa)	paCO2 (on admiss kPa)	Breaths
IMcK	39	M	400	11.1	4.7	304
VB	36	F	200	7.7	4.8	420
KH	21	F	230	8.9	4.0	227
JM	20	F	90	10.4	5.6	356
JA	60	F	200	6.6	5.0	200
EMcC	47	F	200	8.9	4.8	247
CK	21	M	160	7.6	4.7	391
EM	28	F	<60	5.7	4.8	343
AT	21	F	270	8.7	5.6	257
CM	25	M	180	7.5	4.9	213
CHRONIC BRONCHITIS AND EMPHYSEMA						
WF	65	M	180	9.1	6.4	307
RP	75	M	100	10.7	4.7	410
AF	57	M	115	11.1	5.7	321
RD	72	M	100	7.6	4.2	392
EW	53	M	170	9.0	5.1	346
JH	70	M	100	10.7	4.4	357
JD	69	M	220	10.1	3.6	295
WG	68	M	175	8.3	6.4	310
JMcC	79	M	100	7.0	4.5	343
MS	63	F	230	7.8	5.3	283

Pat	PEFR ℓ/min Start	Fin	BREATHS S	F	Vt (ℓ) S	F	Vt/Ti (ℓ/min) S	F	Vt/Ttot (ℓ/min) S	F	Te (secs) S	F	Ttot (secs) S	F	Ti/Ttot S	F	SaO_2 % S	F
IMcK	400	530	304	274	0.44 ±0.08	0.38 ±0.07	22.4 ±4.6	17.7 ±4.9	9.1 ±1.6	7.1 ±1.3	1.75 ±0.32	1.94 ±0.34	2.9 ±0.5	3.2 ±0.5	40.7 ±5.9	40.7 ±6.6	93.9 ±1.7	91.2 ±1.2
VB	200	340	420	406	0.28 ±0.08	0.22 ±0.07	23.6 ±7.1	14.9 ±3.0	7.9 ±2.3	6.0 ±1.4	1.41 ±0.37	1.32 ±0.25	2.1 ±0.4	2.2 ±0.4	34.1 ±7.6	40.2 ±6.1	97.9 ±0.4	96.4 ±0.9
KH	230	290	200	227	0.25 ±0.12	0.18 ±0.11	10.3 ±7.9	6.93 ±4.7	3.73 ±4.62	2.94 ±1.60	2.07 ±1.2	1.96 ±0.86	4.1 ±0.9	3.5 ±0.8	36.6 ±12.2	46.3 ±12.6	97.5 ±1.5	96.1 ±0.5
JM	90	270	356	355	0.34 ±0.06	0.21 ±0.03	16.8 ±3.4	10.7 ±1.8	7.2 ±1.1	4.6 ±0.6	1.59 ±0.26	1.52 ±0.26	2.8 ±0.3	2.7 ±0.3	43.5 ±5.6	44.2 ±6.58	84.53 ±0.52	86.19 ±1.5
JA	200	260	200	220	0.36 ±0.07	0.32 ±0.09	14.9 ±3.3	13.9 ±4.3	5.2 ±0.9	4.8 ±1.6	2.69 ±0.45	2.66 ±0.63	4.1 ±0.6	4.0 ±0.7	35.4 ±6.9	35.3 ±9.26	93.9 ±0.7	92.2 ±0.5
EMc	200	270	247	263	0.53 ±0.14	0.50 ±0.12	30.6 ±5.5	26.4 ±7.8	9.5 ±1.8	8.9 ±2.3	2.34 ±0.56	2.23 ±0.47	2.3 ±0.5	3.4 ±0.6	31.3 ±4.5	35.1 ±6.8	93.2 ±0.6	92.7 ±0.6
CK	160	250	391	350	0.45 ±0.13	0.35 ±0.06	30.9 ±8.1	22.9 ±3.8	12.1 ±4.3	8.3 ±1.3	1.4 ±0.3	1.6 ±0.3	2.3 ±0.5	2.6 ±0.4	37.3 ±7.1	36.9 ±4.9	98.5 ±1.7	98.6 ±0.8
EM	<60	130	343	343	0.33 ±0.03	0.22 ±0.03	23.6 ±4.1	14.4 ±6.4	7.2 ±4.9	5.2 ±0.7	1.5 ±0.3	1.8 ±0.3	2.3 ±0.4	2.6 ±0.2	37.2 ±4.6	33.7 ±3.9	96.6 ±0.8	97.6 ±0.7
AT	270	340	257	278	0.14 ±0.07	0.14 ±0.04	7.2 ±3.4	6.3 ±1.8	2.8 ±1.2	2.6 ±0.7	1.9 ±0.4	1.9 ±0.3	3.1 ±0.5	3.2 ±0.4	39.3 ±6.4	41.8 ±6.7	93.6 ±0.9	91.8 ±1.3
CM	180	230	213	234	1.17 ±0.36	0.91 ±0.34	5.1 ±1.5	3.8 ±1.2	19.1 ±4.8	14.9 ±4.6	2.35 ±1.07	2.36 ±1.21	3.7 ±1.2	3.8 ±1.7	39.2 ±9.9	39.5 ±9.9	93.7 ±2.0	94.1 ±1.8

Pat.	PEFR ℓ/min Start	Fin	Breaths S	F	Vt (ℓ) S	F	Vt/Ti (ℓ/min) S	F	Vt/Ttot (ℓ/min) S	F	Te (secs) S	F	Ttot (secs) S	F	Ti/Ttot S	F	SaO_2% S	F
WF	180	150	307	300	1.72 ±0.62	1.79 ±0.68	9.1 ±3.5	9.9 ±4.0	3.57 ±1.0	3.56 ±1.03	1.69 ±0.54	1.83 ±0.48	2.9 ±0.68	2.98 ±0.63	42.35 ±10.79	30.09 ±10.58	91.24 ±1.52	90.53 ±0.8
RP	100	90	410	389	1.15 ±0.25	0.97 ±0.34	10.0 ±2.7	5.91 ±2.3	3.29 ±0.78	2.63 ±0.7	1.44 ±0.56	1.12 ±0.3	2.17 ±0.65	2.28 ±0.64	34.45 ±9.49	48.59 ±13.29	92.53 ±0.54	90.6 ±0.5
AF	115	165	392	226	2.34 ±0.72	2.20 ±0.86	13.3 ±3.9	13.8 ±5.5	5.13 ±1.77	5.23 ±1.62	1.71 ±0.35	1.54 ±0.41	2.77 ±0.45	2.54 ±0.55	38.82 ±6.68	37.83 ±6.44	94.54 ±1.14	93.3 ±0.76
RD	100	140	321	354	1.58 ±0.84	2.23 ±1.32	12.81 ±6.95	15.96 ±7.21	4.21 ±2.26	4.97 ±3.21	1.52 ±0.56	1.85 ±0.64	2.29 ±0.63	2.72 ±0.66	34.87 ±10.55	32.53 ±12.61	97.73 ±0.44	96.75 ±0.43
EW	170	210	346	369	1.09 ±0.69	1.29 ±0.4	7.03 ±1.87	10.1 ±2.98	2.55 ±0.56	3.24 ±0.92	1.63 ±0.46	1.63 ±0.53	2.59 ±0.52	2.44 ±0.62	36.29 ±7.56	33.65 ±9.62	87.24 ±1.1	88.28 ±0.62
JH	100	110	357	309	1.78 ±0.86	1.66 ±0.82	9.77 ±5.15	8.69 ±4.59	4.49 ±2.68	3.56 ±1.78	1.30 ±0.43	1.57 ±0.63	2.52 ±0.67	2.82 ±0.84	48.10 ±12.81	44.8 ±14.78	95.39 ±2.99	96.99 ±1.54
JD	190	165	295	284	3.4	3.2	13.67 ±9.44	18.18 ±13.5	5.72 ±3.76	8.33 ±8.21	1.71 ±0.55	1.68 ±0.77	3.03 ±0.77	3.13 ±1.0	43.94 ±12.73	47.3 ±14.98	92.93 ±0.41	93.0 ±0.48
WG	130	150	310	286	2.71 ±1.13	1.19 ±0.51	19.95 ±8.86	4.68 ±2.9	6.71 ±3.39	2.37 ±0.84	1.71 ±1.0	1.21 ±0.61	2.64 ±1.05	3.0 ±0.89	37.7 ±17.67	59.54 ±17.23	91.86 ±1.55	92.46 ±1.04
JMc	100	165	343	295	4.46 ±1.12	5.74 ±1.04	29.01 ±14.3	31.3 ±5.53	11.53 ±4.5	11.48 ±2.17	1.42 ±0.39	1.92 ±0.40	2.62 ±0.74	3.02 ±0.56	44.17 ±13.16	37.09 ±6.32	87.81 ±2.79	76.67 ±3.34
MS	230	240	283	273	0.15 ±0.06	0.15 ±0.06	7.42 ±3.34	7.88 ±3.31	2.97 ±1.34	2.86 ±1.17	1.83 ±0.54	2.02 ±0.53	3.16 ±0.75	3.22 ±0.68	42.47 ±12.27	38.02 ±0.68	96.36 ±0.64	94.64 ±0.94

CHAPTER 5

The effect of bronchodilatation on peak expiratory flow rate and breathing patterns in acute asthma

In the previous study bronchodilatation was associated with falls in tidal volume, minute ventilation, and inspiratory drive as measured by an inductive plethysmograph. The changes in breathing pattern observed may have been due at least, in part, to the bronchodilator used, namely the beta-2 sympathomimetic agent, terbutaline. In order to determine whether bronchodilatation alone caused these changes in breathing pattern, and to determine whether a different bronchodilator therapy conferred any advantage in the treatment of acute asthma, a further study of acute asthmatic patients was carried out.

Inhaled beta-2 agonists (Choo-Kang et al, 1970) and more recently the anticholinergic drug Ipratropium bromide (Ward et al, 1981; Ward et al, 1985) are both known to relieve airflow limitation in acute severe asthma. Furthermore, it has been suggested that larger than conventional doses of beta-2 agonist drugs or Ipratropium would be of benefit in treatment of the acute asthmatic attack (Blackhall et al, 1976; Ward et al, 1981). Studies with Ipratropium bromide have been carried out in healthy volunteers (Bleichert, 1975; Weisser, 1975) and in acute asthma (Allan and Campbell,

1980; Ward et al 1981) and no ill effects observed (Table 8). Large doses of Ipratropium bromide have produced no significant changes in pulse rate, blood pressure or salivation (Bleichert, 1975; Weisser, 1975) but this was in normal volunteers and not in the acute asthmatic. The beta-2 agonist fenoterol has similar bronchodilator effects to salbutamol and terbutaline, but is thought to have a more prolonged duration of action (Petit & Roberts, 1973). The dose of 2.5mgs fenoterol has been shown to be equivalent to 10mgs of nebulised terbutaline and was again not associated with excessive side effects (Carmichael et al, 1980; Blackhall et al, 1976).

Therefore the inductive plethysmograph was used to record breathing patterns, along with ear oxygen saturation and peak expiratory flow rate, in 30 patients admitted with acute severe asthma. They received treatment with either inhaled fenoterol, or inhaled ipratropium bromide, or both drugs in combination, each regime being applied in 10 of the patients.

METHODS

Patients

Thirty patients with acute asthma were studied in each of whom the heart rate was over 100 beats per minute, and peak expiratory flow rate (PEFR) less than

60% of their best out-patient value. Their mean PEFR on admission was 60-340 litres/min (mean 193 litres/min). All patients were subsequently shown to increase their FEV_1 by >20% with an inhaled beta-2 agonist when in a clinically stable state following the acute attack. Measurement of PEFR, blood gas tensions, and breathing pattern as recorded by the respiratory inductive plethysmograph were always started within 18 hours following admission to hospital, with an average six hours between starting the study and admission. All were admitted due to an attack of acute severe asthma but nebulised or intravenous bronchodilator therapy had not been given for four hours before starting the inductive plethysmograph measurements. 12 of the 30 patients had received a 250mg intravenous bolus of aminophylline on admission, but the study started at least four hours later. None received continuous infusions of theophylline. All were given 250mg of hydrocortisone IV on admission, and 40mg per day of prednisolone by mouth thereafter. All were given at least 2l/min of oxygen by nasal prongs throughout the study.

Treatment

The 30 patients were randomly allocated to one of three treatment regimens (Table 9). Ten inhaled 2.5mg of fenoterol (F), 10 inhaled 500ug of ipratropium (I) and 10 2.5mg fenoterol combined with 500 ug of

ipratropium (F+I). All nebuliser solutions were made up to 2.5ml with 0.9% saline, and were nebulised to dryness in a Wright's nebuliser driven by 4l/min of oxygen.

Procedure

Peak expiratory flow rates (PEFR) were measured by mini-Wright peak flow meter (Wright & Mckerrow, 1959) at the start of the study, and every 30 minutes for 90 minutes after the start of nebulisation. Breathing patterns were recorded by an inductive plethysmograph. One band was taped securely at the level of the 2nd-4th intercostal space anteriorly, the other at the level of the umbilicus, and the calibration procedure carried out as previously described in Chapter 3. Ear oxygen saturation was measured by the Hewlett-Packard 47201A ear oximeter (Douglas et al, 1979). Chest wall amplitude, respiratory rate, ear oxygen saturation and heart rate were recorded on line, breath by breath, using a MINC 11 computer at the bedside. Initial data was collected for 15 minutes before administering the selected nebuliser therapy. Breathing patterns, oxygen saturation and heart rate were then continuously monitored for a further 90 minutes. Values obtained during the initial 0-15 minute period before nebulisation were compared with data obtained between the 75th and 90th minutes after nebulisation, unless otherwise stated. Values are given as mean and standard

error, the significance of difference being determined by paired t test, or by analysis of variance and Duncan's multiple comparison test (Snedecor & Cochrane, 1980). All patients gave informed consent to the study, which was approved by the Hospital Ethical Committee.

Results (Table 10)

Peak expiratory flow rate increased with all three treatment regimens, at both 30, 60 and 90 minutes after nebulisation (Fig 13). However, the mean peak expiratory flow rate in those receiving fenoterol alone (165±201/min), although similar to that in the patients treated with ipratropium (196±381/min) was significantly lower than the initial peak expiratory flow rate in those randomly allocated to treatment with a combination of fenoterol and ipratropium (218±21/min) (Table 10). Thus, although the 10 patients receiving both drugs by nebulisation showed a greater increase in peak expiratory flow rate 90 minutes after nebulisation, than in those receiving either drug alone, this was not significantly different between any of the three treatment regimens. None of the treatment regimens produced any significant change in heart rate.

There were no significant changes in breathing frequency or respiratory timing, (Ti/Ttot) by 90 minutes after nebulisation in any of the three treatment groups. However, by that time resting ventilation had fallen significantly ($p<0.05$, Figure 14) by 13% after F and 16%

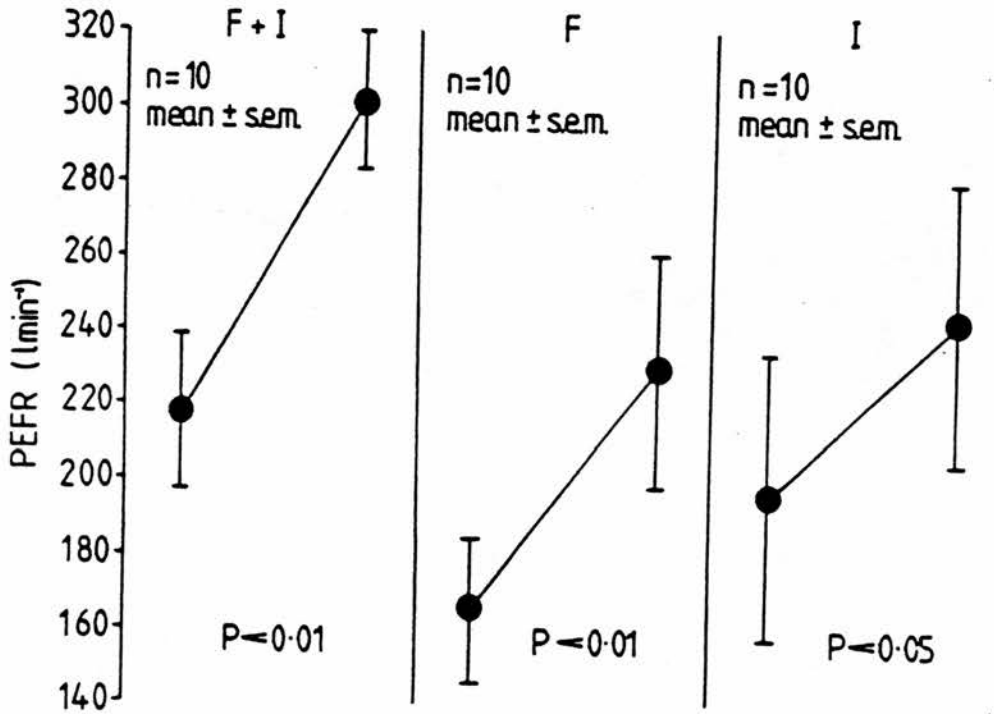

Figure 13 Effect of three different treatments on peak expiratory flow rate at 90 minutes. F = Fenoterol, I = Ipratropium bromide.

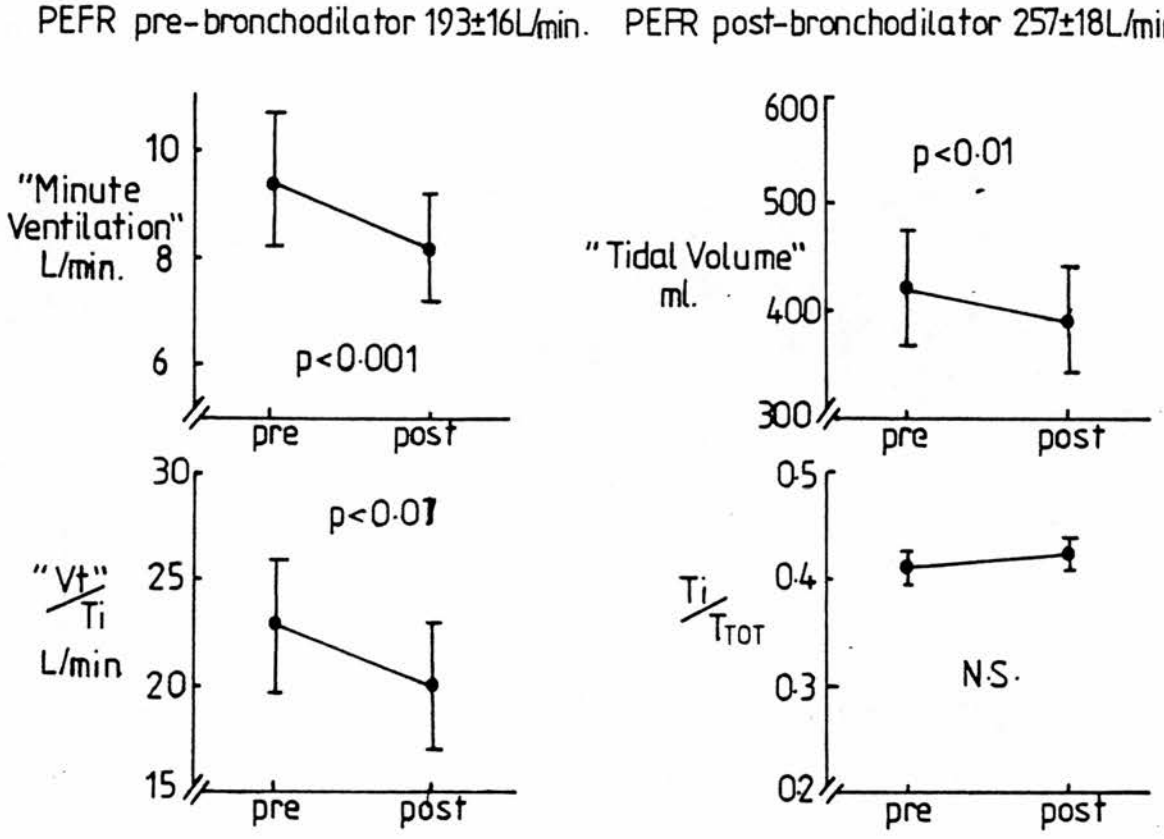

Figure 14 Effect of bronchodilatation on ventilation, tidal volume, inspiratory drive and the respiratory duty cycle (Ti/Ttot) in all patients. (n=30, mean±SEM).
PEFR pre bronchodilator - 193±6L/min
PEFR post bronchodilator - 257±8L/min.

after F+I and although ventilation fell after treatment with ipratropium by 13% this did not reach statistical significance. Similarly, Vt/Ti fell in all three treatment groups by 15+5 after F, 15+5% after F+I ($p<0.05$) and 16+5% after ipratropium but this did not reach significance (Figure 15). There was no significant difference between any of the treatment groups in the changes in any of these respiratory variables.

Combining all three treatment groups peak expiratory flow rate rose by more than 20% at 90 minutes in 20 of the 30 patients studied, with falls in ventilation, inspiratory drive and tidal volume (Figure 14). Peak expiratory flow rate rose by less than 20% on inhalation in the remaining 10 patients (designated as "non-responders") mean initial peak expiratory flow rate 223+ 35 l/min, 90 minutes 230+35 l/min) three of whom received fenoterol, four ipratropium and three the combination. Despite this lack of improvement in peak expiratory flow rate these 10 patients showed similar improvements in breathing pattern to those in patients in whom peak expiratory flow rate rose by more than 20%, with significant falls in minute ventilation and inspiratory drive (Figure 16).

All patients received supplemental oxygen therapy and no significant changes were seen in oxygen

saturation.

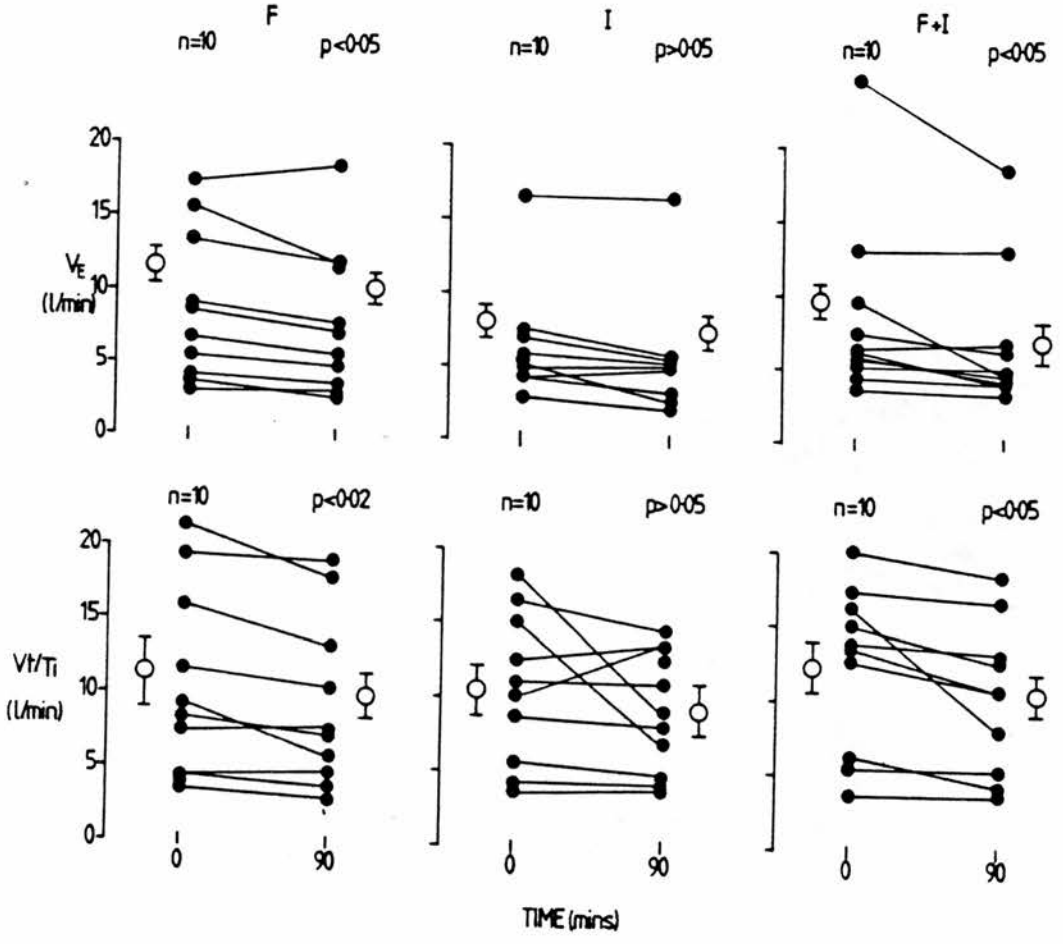

Figure 15 Changes in ventilation and inspiratory drive in each of the three treatment groups.

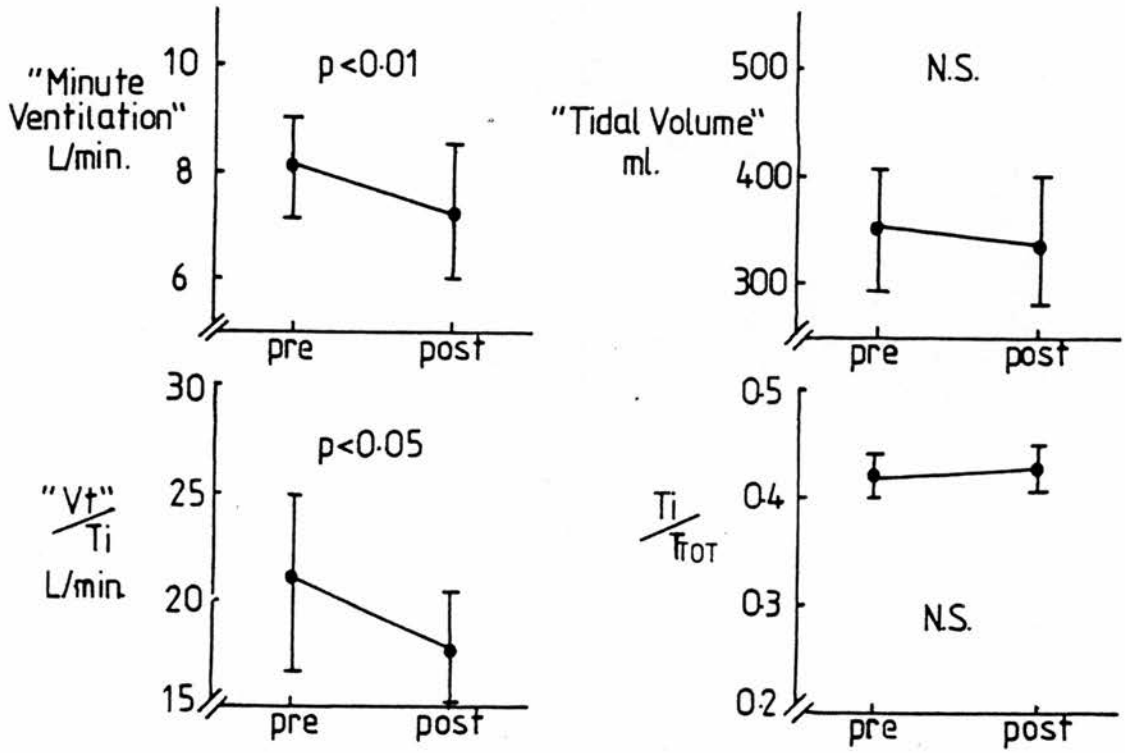

Figure 16 Changes in ventilation, tidal volume, inspiratory drive and respiratory duty cycle in 10 acute patients in whom PEFR did not rise by more than 20% ("non responders"). n = 10, mean±SEM.
PEFR pre bronchodilator - 223±35L/min
PEFR post bronchodilator - 230±35L/min.

Discussion

The effects of two different types of bronchodilator (beta-2 agonist and anti-cholinergic), were measured, separately and in combination, on peak expiratory flow rate and breathing patterns in acute asthma. Both agents alone, and in combination, increased peak expiratory flow rate 90 minutes after nebulisation, but there were no significant differences in the effect of bronchodilatation achieved by the three treatments. Both minute ventilation and inspiratory drive fell to a similar extent with each treatment.

This study confirms that ventilation was increased and $PaCO_2$ reduced in acute asthma (Hudstrand, 1971). Previous results in stable asthmatics have shown that central respiratory drive to CO_2 (as measured by mouth occlusion pressure, P 0.1) is higher in the stable asthmatic than in normal subjects (Zakon et al, 1976). This is supported by the current study showing that inspiratory drive (Vt/Ti) falls in response to treatment in acute asthma. This increased Vt/Ti as measured by inductive plethysmography in symptomatic asthmatic patients has already been described [Tobin et al, 1983 (i)]. Peak expiratory flow rate rose by less than 20% after therapy in 10 of the 30 patients studied. However, these 10 patients still showed similar changes in minute ventilation and inspiratory drive to those in the other 20 patients in whom peak expiratory rate rose

by more than 20%. It has previously been noted that significant symptomatic improvement may occur in asthmatics following bronchodilator therapy despite any evidence of increased forced expiratory flow rates (Douglas et al, 1985; Woolcock and Read, 1965). Bronchoconstriction is associated with increases in both resistive and elastic inspiratory muscle work (Martin et al, 1983) and the elastic component may be diminished reducing the degree of hyperinflation without producing changes in airway calibre as assessed by peak expiratory flow rate or FEV_1 (Woolcock and Read, 1965). The observed falls in minute ventilation and inspiratory drive seen in the group of patients in whom peak expiratory flow rate did not rise significantly may reflect this change in lung volume.

No significant difference in the bronchodilator response between the beta-2 agonist and the atropine like drug nor any additional benefit from combining both drugs was found. Previous studies have also demonstrated similar bronchodilator responses to beta-2 agonists and atropine like drugs in asthma (Petrie and Palmer, 1975). It has been suggested in acute asthma (Ward et al, 1981; Ward et al, 1985) and in patients with stable chronic bronchitis and emphysema (Douglas et al, 1979) that the combination of a beta-2 agonist and an atropine like drug may be more effective than either agent alone. This interaction could not be confirmed in the current study, perhaps because the patients had

improved by the time the study started and so near maximal bronchodilatation could be achieved with either agent alone. Thus all three inhaled drug regimens produced effective bronchodilatation of similar degree 30,60, and 90 minutes after nebulisation and there were similar falls in ventilation and inspiratory drive as previously observed in acute asthmatic patients treated in a conventional manner (Chapter 4). There was no significant difference in bronchodilatation as measured by peak expiratory flow rate between any of the three treatment groups. It is of interest to note that in 10 patients in whom peak expiratory flow rate did not rise by 20%, there were however similar falls in minute ventilation and inspiratory drive as seen in the other 20 patients. Furthermore, although the drug ipratropium alone produced similar bronchodilatation, with similar falls in minute ventilation and inspiratory drive, these did not reach statistical significance. Further investigation is required to establish whether changes in minute ventilation and inspiratory drive are more sensitive than changes in peak expiratory flow rate in monitoring the clinical response of patients with acute asthma.

TABLE 8

REPORTED SIDE EFFECTS OF INHALED BRONCHODILATORS TO BE STUDIED

FENOTEROL

Diagnosis	No of patients	Age	Dose	Side effects	Source
Asthma	10	9.8 (6-14)	2mg	tremor(1)	Blackhall et al (1976)
Asthma	12	52 (24-73)	1mg 2mg	tremor(3) tremor(5)	Carmichael et al (1980)

IPRATROPIUM

Diagnosis	No of patients	Age	Dose	Side effects	Source
Asthma	10	adult	120µg	nil	Allen et al (1980)
Acute asthma	22	40	250µg 750µg	nil nil	Ward et al (1981)
Healthy men	12	adult	800µg	nil	Bleichert (1975)
Healthy men	24	31 (19-51)	280µg	nil	Weiser (1975)

TABLE 9

PATIENT DATA: ACUTE ASTHMA

FENOTEROL

Patient	Age (yrs)	Sex	PEFR on adm. ℓ/min	pa02 on air	paCO2 kPa	Breaths
EP	49	F	100	5.4	4.9	335
MP	65	F	80	9.3	3.7	539
MH	67	F	130	9.0	3.8	409
LQ	17	F	100	8.5	5.3	230
HR	59	F	160	7.0	4.7	360
ED	16	F	180	8.9	4.7	221
BW	34	F	250	9.0	6.1	271
AS	23	F	260	9.2	3.6	183
SG	17	F	200	7.5	3.3	327
RC	54	M	190	7.6	5.3	276

TABLE 9 (contd)

IPRATROPIUM

Patient	Age (yrs)	Sex	PEFR on adm. ℓ/min	pa02 on air	paCO2 kPa	Breaths
MB	52	F	120	7.5	5.7	298
AS	44	F	60	5.7	4.8	274
ML	52	F	330	8.4	5.3	241
AS	56	M	210	8.0	4.8	287
HP	16	F	200	9.2	5.1	192
AW	18	F	100	7.5	6.4	264
JK	59	M	340	10.6	4.6	221
RS	17	M	260	8.3	5.8	223
CM	21	F	80	8.3	5.8	223
JB	40	F	160	11.1	4.9	297

TABLE 9 (contd)

FENOTEROL + IPRATROPIUM

Patient	Age (yrs)	Sex	PEFR on adm. ℓ/min	pa02 on air kPa	paCO2	Breaths
MB	60	F	220	9.1	4.6	395
HMcD	35	F	280	8.4	4.4	259
JG	18	F	110	8.7	5.6	314
PM	44	M	240	8.9	4.3	220
EM	28	F	240	9.1	6.6	353
CK	21	M	140	6.5	4.4	335
SS	16	F	240	7.7	5.2	294
CM	16	F	165	9.5	4.2	246
VB	38	F	340	9.1	4.6	286
DY	49	F	200	8.9	4.8	257

RESULTS

FENOTEROL

Pat.	PEFR (ℓ/min) Start	Fin.	Breaths S	F	Vt (ℓ) S	F	V_t/T_i (ℓ/min) S	F	Vt/Ttot (ℓ/min) S	F	Te (secs) S	F	Ttot (secs) S	F	T_i/Ttot S	F	SaO_2% S	F
EP	100	200	335	302	0.63 ±0.17	0.74 ±0.13	4.2 ±1.7	4.6 ±1.0	16.5 ±5.7	18.0 ±3.5	1.46 ±0.38	1.53 ±0.32	2.51 ±0.57	2.52 ±0.42	41.5 ±10.2	39.5 ±6.2		
MP	80	90	539	434	0.17 ±0.06	0.16 ±0.04	15.9 ±5.1	12.8 ±4.7	6.2 ±1.6	5.1 ±1.6	0.99 ±0.46	1.18 ±0.47	1.67 ±0.57	2.05 ±0.63	41.1 ±9.5	42.2 ±11.8		
MH	130	150	409	333	0.44 ±0.08	0.41 ±0.12	41.1 ±8.4	32.8 ±13.8	13.6 ±2.3	12.2 ±3.7	1.37 ±0.40	1.49 ±0.34	2.05 ±0.46	2.70 ±2.30	33.1 ±5.8	37.2 ±14.2	95.1 ±0.43	94.3 ±2.4
LQ	100	105	230	270	0.24 ±0.06	0.19 ±0.03	11.5 ±2.3	10.2 ±1.7	4.1 ±0.7	3.6 ±0.7	2.37 ±0.49	2.14 ±0.27	3.64 ±0.64	3.30 ±0.32	35.1 ±4.9	35.3 ±4.6	88.32 ±0.79	90.3 ±0.62
HR	160	180	360	289	0.32 ±0.1	0.33 ±0.12	21.5 ±5.8	17.6 ±7.0	8.6 ±2.1	6.9 ±2.4	1.39 ±0.27	1.84 ±0.56	2.33 ±0.42	3.05 ±1.16	40.0 ±6.7	39.2 ±7.7	91.6 ±0.6	91.3 ±1.0
ED	180	330	221	174	0.99 ±0.27	0.98 ±0.29	36.6 ±11.6	27.1 ±11.3	15.6 ±4.3	12.0 ±3.2	2.36 ±0.49	2.84 ±0.65	4.08 ±0.73	5.07 ±1.05	42.2 ±6.11	44.3 ±6.3	97.0 ±1.0	97.0 ±0.5
BW	250	370	271	322	0.46 ±0.26	0.45 ±0.17	19.1 ±15.2	18.7 ±7.3	8.2 ±5.4	7.6 ±2.6	1.81 ±0.46	1.66 ±0.45	3.33 ±0.66	2.79 ±0.56	45.3 ±9.7	40.8 ±7.3	95.0 ±0.61	92.5 ±0.9
AS	260	350	183	202	0.37 ±0.07	0.34 ±0.09	13.3 ±3.0	11.9 ±3.1	5.3 ±1.0	4.8 ±0.9	2.63 ±0.82	2.67 ±0.93	4.41 ±1.32	4.46 ±1.45	40.2 ±4.8	40.2 ±5.9	96.8 ±0.5	95.8 ±0.7
SG	200	250	327	312	1.37 ±0.35	1.36 ±0.35	73.9 ±13.2	74.9 ±20.9	29.4 ±5.1	28.4 ±9.1	1.69 ±0.34	1.79 ±0.19	2.77 ±0.36	2.89 ±0.22	39.3 ±4.6	37.9 ±4.0	93.8 ±1.28	95.6 ±0.99
RC	190	260	276	330	0.18 ±0.09	0.11 ±0.03	8.8 ±3.7	5.48 ±1.9	3.6 ±1.6	2.5 ±0.9	1.69 ±0.36	1.44 ±0.39	2.93 ±0.69	2.71 ±0.61	41.8 ±8.7	46.6 ±10.4	92.2 ±1.0	94.0 ±1.1

TABLE 10 (contd)

RESULTS IPRATROPIUM

Pat	PEFR (ℓ/min) Start	Fin.	Breaths S	F	Vt(ℓ) S	F	Vt/T_i(ℓ/min) S	F	Vt/Ttot (ℓ/min) S	F	Te (secs) S	F	Ttot S	F	T_i/Ttot S	F	$Sa0_2$ % S	F
MB	120	150	298	342	0.16 ±0.08	0.14 ±0.02	8.7 ±2.9	8.1 ±1.54	3.9 ±1.7	3.2 ±0.5	1.35 ±0.32	1.56 ±0.27	2.51 ±0.58	2.63 ±0.37	46.1 ±12.4	40.7 ±5.9	98.9 ±1.9	95.1 ±0.6
AS	60	100	274	288	0.32 ±0.10	0.28 ±0.06	16.7 ±6.8	14.5 ±3.4	6.5 ±2.7	5.4 ±1.3	1.85 ±0.53	1.93 ±0.43	3.05 ±0.72	3.10 ±0.55	40.0 ±9.8	38.2 ±8.0	96.9 ±1.1	96.0 ±0.9
NL	430	435	241	283	0.38 ±0.11	0.26 ±0.07	18.2 ±7.9	9.0 ±4.5	7.0 ±2.8	5.1 ±1.9	2.07 ±0.58	1.27 ±0.36	3.42 ±0.70	3.17 ±0.59	40.5 ±9.3	59.8 ±10.6	96.9 ±0.6	97.6 ±0.6
AS	210	200	287	290	0.81 ±0.12	0.79 ±0.13	40.2 ±8.5	38.5 ±8.4	16.3 ±4.0	16.2 ±3.7	1.85 ±0.34	1.78 ±0.28	3.12 ±0.49	3.09 ±0.48	40.8 ±6.7	42.4 ±6.4		
HP	200	240	192	270	0.34 ±0.11	0.26 ±0.08	11.5 ±4.5	11.3 ±3.8	5.7 ±1.5	5.2 ±1.8	2.13 ±0.85	1.65 ±0.70	3.85 ±1.02	3.01 ±0.81	49.5 ±14.9	46.7 ±13.3	91.1 ±3.7	95.1 ±2.9
AW	100	260	264	292	0.25 ±0.07	0.26 ±0.10	12.6 ±3.9	13.5 ±5.2	4.7 ±1.2	5.3 ±1.7	1.96 ±0.31	1.85 ±0.29	3.18 ±0.35	3.06 ±0.38	38.3 ±5.4	39.5 ±4.4	93.6 ±1.8	92.3 ±1.8
JK	340	460	221	252	0.29 ±0.09	0.15 ±0.08	14.9 ±4.8	6.7 ±3.5	4.8 ±1.9	2.5 ±1.3	2.56 ±0.89	2.5 ±1.3	3.79 ±0.98	3.59 ±0.76	33.0 ±6.7	37.6 ±8.1	92.7 ±0.7	93.8 ±0.7
RS	260	220	223	215	0.15 ±0.07	0.12 ±0.02	3.5 ±1.5	3.9 ±0.8	2.5 ±0.4	1.7 ±0.2	1.89 ±0.42	2.23 ±0.35	3.61 ±0.44	4.17 ±0.54	47.5 ±9.8	46.8 ±6.8	86.3 ±1.1	89.3 ±0.6
CM	80	120	386	424	0.94 ±0.20	0.75 ±0.13	56.3 ±12.3	47.7 ±9.6	27.0 ±4.1	21.3 ±3.1	1.10 ±0.23	1.17 ±0.19	2.09 ±0.35	2.12 ±0.27	47.6 ±8.6	45.2 ±4.4	92.6 ±0.6	90.7 ±2.0
JB	160	260	297	323	0.17 ±0.04	0.18 ±0.04	10.2 ±3.1	13.6 ±5.9	3.9 ±0.9	5.0 ±1.1	1.66 ±0.37	1.73 ±0.85	2.72 ±0.53	2.77 ±0.91	38.7 ±9.2	37.1 ±18.7	95.3 ±0.9	96.6 ±1.2

TABLE 10 (contd)

RESULTS

FENOTEROL AND IPRATROPIUM

Pat	PEFR (ℓ/min) Start	Fin	Breaths S	F	Vt (ℓ) S	F	Vt/Ti (ℓ/min) S	F	Vt/Ttot (ℓ/min) S	F	Te (secs) S	F	Ttot (secs) S	F	Ti/Ttot S	F	SaO% S	F
MB	220	300	395	322	0.18 ±0.09	0.20 ±0.16	13.2 ±6.5	10.7 ±8.7	5.6 ±3.0	4.6 ±2.6	1.21 ±0.57	1.55 ±0.62	2.08 ±0.76	2.74 ±0.82	42.2 ±11.3	42.5 ±13.2	95.3 ±0.8	96.7 ±0.5
HMcD	280	290	259	255	0.76 ±0.12	0.77 ±0.11	3.7 ±0.6	3.7 ±0.6	13.3 ±2.0	13.3 ±1.9	2.23 ±0.35	2.29 ±0.36	3.47 ±0.46	3.53 ±0.49	35.9 ±5.5	35.1 ±5.6	93.6 ±0.8	95.2 ±0.7
JG	110	250	314	343	0.83 ±0.25	0.76 ±0.13	6.2 ±1.2	4.4 ±1.9	24.5 ±8.6	18.4 ±4.4	1.62 ±0.45	1.54 ±0.33	2.56 ±0.65	2.63 ±0.43	39.4 ±13.3	41.5 ±7.9		
PM	240	380	220	286	0.39 ±0.16	0.33 ±0.20	17.3 ±5.3	16.6 ±9.81	6.3 ±2.2	6.61 ±4.1	2.43 ±0.79	1.89 ±0.63	3.69 ±0.68	3.05 ±0.61	37.0 ±6.5	39.7 ±9.2	94.1 ±0.5	94.0 ±0.4
EM	240	260	353	365	0.13 ±0.02	0.20 ±0.14	13.6 ±2.2	12.8 ±7.0	5.2 ±0.9	4.9 ±4.0	1.47 ±0.22	1.53 ±0.46	2.37 ±0.25	2.47 ±0.59	38.1 ±5.2	38.2 ±6.4	92.4 ±0.8	91.7 ±0.6
CK	140	270	335	289	0.27 ±0.05	0.20 ±0.09	16.4 ±3.9	7.8 ±3.9	9.5 ±1.4	4.5 ±1.8	1.47 ±0.24	1.26 ±0.41	2.50 ±0.31	3.12 ±0.85	41.0 ±6.7	58.1 ±12.8	98.1 ±1.0	94.4 ±0.87
SS	240	320	294	289	0.28 ±0.07	0.23 ±0.3	15.1 ±3.5	12.6 ±1.3	5.9 ±1.4	4.5 ±0.6	1.75 ±0.39	1.96 ±0.23	2.86 ±0.44	3.06 ±0.26	39.2 ±5.2	36.1 ±3.2	93.9 ±0.7	94.5 ±0.7
CM	165	215	246	271	0.41 ±0.03	0.35 ±0.04	19.9 ±1.9	18.2 ±2.9	7.5 ±0.6	6.4 ±0.4	2.05 ±0.19	2.17 ±0.29	3.28 ±0.23	3.32 ±0.29	37.7 ±2.5	34.9 ±4.1	89.1 ±0.4	85.2 ±0.8
VB	340	370	286	345	0.17 ±0.05	0.14 ±0.07	5.8 ±4.2	5.6 ±1.0	3.7 ±3.2	3.1 ±0.8	0.88 ±0.31	1.10 ±0.34	2.81 ±1.69	2.61 ±0.89	64.7 ±13.7	56.0 ±12.0	91.9 ±0.9	95.5 ±1.11
DY	200	360	257	321	0.24 ±0.06	0.20 ±0.03	12.8 ±3.6	10.8 ±2.7	4.8 ±1.2	4.5 ±0.8	1.97 ±0.43	1.62 ±0.42	3.15 ±0.53	2.81 ±0.62	37.5 ±7.7	42.2 ±7.9	97.1 ±1.4	92.9 ±1.0

CHAPTER 6

The effect of bronchial challenge on breathing patterns and oxygenation in stable asthma

In previous chapters, bronchodilatation in acute asthmatic patients produced parallel falls in minute ventilation and inspiratory drive. Thus, if these changes are associated with bronchodilatation, do reciprocal changes occur with the onset of bronchoconstriction? To examine this, a study was carried out of breathing patterns and oxygen saturation in stable asthmatic patients in whom bronchoconstriction was induced by means of inhalation challenge testing with either histamine or methacholine.

Since Tiffeneau introduced the concept of an inhalation challenge procedure with histamine as a diagnostic test for asthma in 1958, many different methods of testing have been developed (Chai et al, 1985; Cockcroft et al, 1977 (i), Yan et al, 1983; Britton et al 1986). The method described by Cockcroft et al, [1977 (i)] using the Wright nebuliser, however, is well standardised and has been widely adopted. Hyper-reactivity of the airways to inhaled bronchoconstrictor agents is widely used to diagnose asthma, both in clinical practice (Cockcroft et al, 1977 (ii); Makino, 1966) and epidemiological studies (Cockcroft et

al, 1977 (i); Lam et al, 1979; Townley et al, 1975; McQueen et al, 1979; Lee et al, 1983) and to study the mechanisms of asthma (Empey et al, 1976).

Non allergic (non-specific) airway responsiveness to histamine and methacholine is increased in virtually all, if not all, subjects with current symptoms of asthma (Cockcroft et al, 1979). The degree of increase is related to the severity of the symptoms (Makino, 1966), the number of previous hospital admissions (Townley et al, 1975), and the ease with which asthma is induced by non-allergic (Eggleston, 1979; Anderson et al 1979; Horton et al, 1978) and allergic stimuli (Cockcroft et al, 1979). Methacholine inhalation challenge has been shown to give similar results to histamine challenge (Spector & Farr 1975; Juniper et al, 1981) and be more sensitive than exercise challenge (Eggleston, 1979; Kwiloog, 1973).

Most previous studies of the effect of bronchial challenge on breathing patterns have used either masks or mouthpieces (Mann et al, 1978; Savoy et al, 1981; Kelsen et al, 1981; Pardy et al, 1979) but these are known to affect the breathing pattern (Gilbert et al, 1972). Furthermore, histamine induced broncho-constriction is known to produce mild hypoxia (Poppius & Stenius, 1977) but the mechanism of this is unclear. To examine the effect of bronchoconstriction on breathing patterns non-invasively the inductive plethysmograph has

been used to measure ventilation and breathing pattern along with ear oxygen saturation in stable asthmatic patients during bronchial challenge.

METHODS

Patients

Ten male asthmatics aged 17-61 yr (mean age 36) (Table 11), all of whom could increase their FEV_1 by at least 20% following the inhalation of a B_2 agonist, were studied. All were in a stable clinical state at the time of study, with no exacerbation of their asthma for at least six weeks. Their base-line FEV_1 ranged from 1.3-2.6 litres with a mean 2.3 litres before the study. Five had positive skin reactions to grass pollens, dermatophagoides pteronyssinus, and/or cat fur. All were being treated with regular inhaled B_2 agonists, and three patients also received 5-10mg prednisolone daily by mouth. Three other patients were receiving oral theophyllines, but these were discontinued for at least 24 hours before the study. B_2 agonists by inhalation were also withheld for at least 8 hours before each study. No patient was receiving sodium cromoglycate.

Bronchial Challenge

All patients were challenged with histamine on one day and methacholine on another day, using the method described by Cockcroft et al [1977 (i)]. A Wright's nebuliser was driven by a compressed airflow of 7

litres/minute at 52lbs per square inch to nebulise 5ml of test solution over 2 minutes, thus producing an output of 0.12ml/min with a particle size of 1.5 um mass median diameter. The control solution was 0.9% normal saline, with histamine as Histamine acid phosphate and methacholine being acetyl-beta-methylcholine chloride made up in solutions of 0.03, 0.06, 0.125, 0.25, 0.5, 1,2,4,8 and 16 mgs/ml. Solutions were stored at 4 °C. FEV_1 was measured by a dry spirometer. Initial FEV_1 measurement was taken at least three times or until it was reproducable to within 3%. The FEV_1 had to be above one litre and preferably greater than 70% of predicted or greater than 70% of the patients best. The control solution (0.9% normal saline) was inhaled through a face mask loosely held over the nose and mouth with a noseclip applied. The subject breathed in a relaxed way by tidal mouth breathing for two minutes, and then FEV_1 measured at 30 and 90 seconds. If there was a fall in FEV_1 at 90 seconds, which is the same or lower than that at 30 seconds the measurement would be repeated at 3 minutes and then subsequent 2 minute intervals until the FEV_1 starts to rise again. The FEV_1 was measured only once on each occasion unless it was not technically satisfactory, when it was measured straight away. If the FEV_1 falls by 20% or more, or to below one litre, the test is discontinued. If however the FEV_1 was still within 20% of the initial value, the patient then inhaled the doubling concentration of either histamine

or methacholine for two minutes, every five minutes.

The starting concentration should be 0.03 mg/ml, but with practice this can be predicted from baseline spirometry, the response to the control inhalation and the recent treatment required to control symptoms as follows

FEV_1 >70% predicted and FEV_1 falls <10% following control inhalation

Inhaled or ingested corticosteroids	0.125mg/ml
daily bronchodilators	0.25
Occasional bronchodilators (<once/day)	1.0
No medications	2.0

or

FEV_1 <70% predicted and FEV_1 falls <10% following control inhalation

Inhaled or ingested corticosteroids	0.03mg/ml
Other medications	0.125mg/ml

or

FEV_1 falls >10% following control inhalation

All subjects	0.03mg/ml

When FEV_1 fell by more than 20% following inhalation the patient then took 2 puffs (200ug) of salbutamol from a pressurised aerosol.

Calculation of Results

The per cent fall in FEV_1 post histamine or methacholine is calculated from the formula

$$\frac{\text{Lowest FEV1 (PS)} - \text{lowest FEV1 (post H or M)}}{\text{lowest FEV1 (PS)}} \times 100$$

or methacholine x 100

where PS = post saline

H = histamine

M = methacholine

From this the PC20 (provocation concentration which will cause a fall in FEV_1 of 20%) is calculated from the last 2 points on the log-dose response curve (Figure 17).

Interpretation of Results

From the PC20's the scale of the extent of bronchial hyper-reactivity and thus the severity of asthma can be demonstrated thus

Severely increased - FEV_1 falls >20% on 0.025mgs or less: PC20 <0.25mgs/ml

Moderately increased - FEV_1 falls 20% or more on 0.25-1.0 mg: PC20 0.25-<2.0 mg/ml

Mildly increased - FEV_1 fall of 20% or more on 2.0-8.0 mg/ml: PC20 2.0-8.0 mg/ml

Normal - FEV_1 falls <20% on 8.0 mg/ml: PC20 >8.0mg/ml.

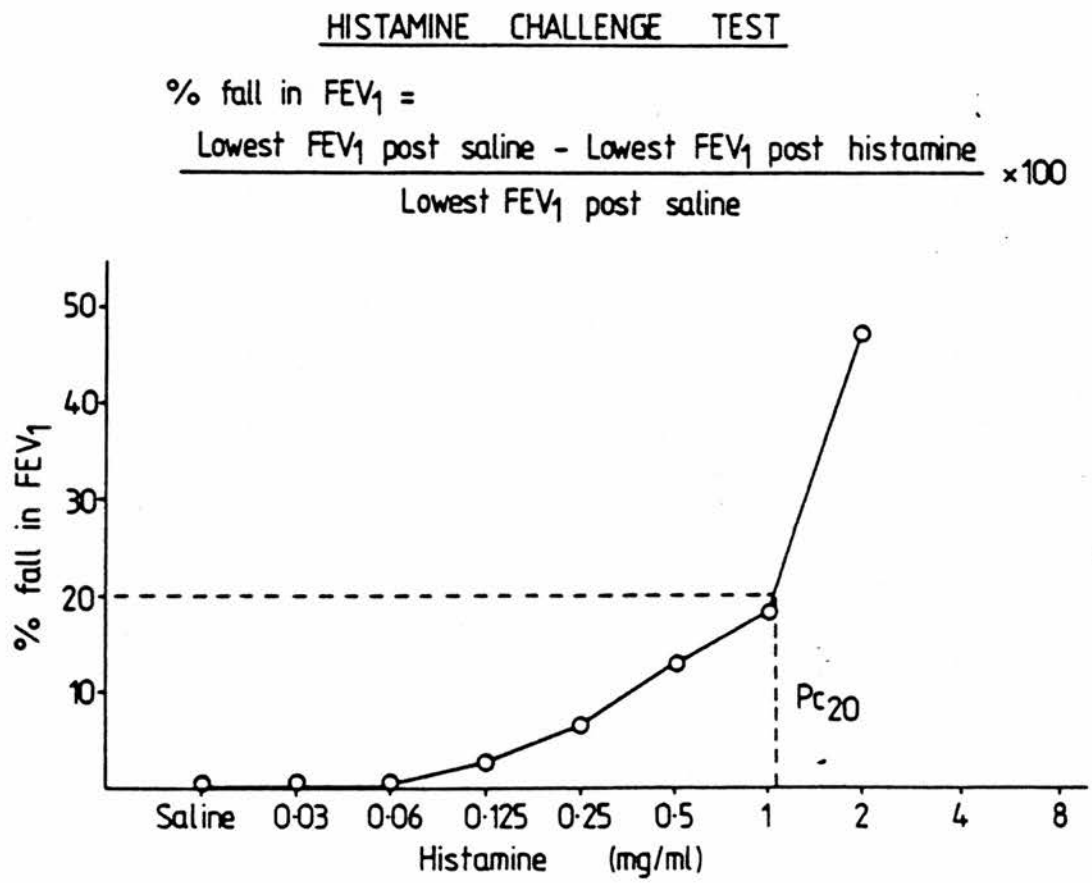

Figure 17 Histamine challenge test.

Measurements

Breathing patterns were measured using a respiratory inductive plethysmograph. As before, one band was taped securely around the rib cage at the second to fourth intercostal space anteriorly and the other around the abdomen at the level of the umbilicus. The relative gains of the chest and abdominal bands were arbitrarily fixed to be unity, and the sum of these two signals was then calibrated as the patient gently inflated a 600ml bag. Breathing patterns were recorded for four minutes before the first bronchial challenge, then from one and a half to five and a half minutes following the inhalation of the dose of histamine which produced a 20% or greater fall in FEV_1. Breathing patterns were again recorded between 2-6 minutes after the inhalation of salbutamol. All periods of recording breathing patterns excluded occasions when the FEV_1 was being measured. The arterial oxygen saturation was recorded throughout, by an ear oximeter.

To investigate the accuracy of the inductive plethysmograph after the induction of broncho-constriction, the sum of the inductive plethysmograph signals to the tidal volume as measured by a water sealed spirometer, before and after histamine challenge in 4 patients, was compared on a separate occasion. The ratio of the sum of the Respitrace signals to the tidal volume measured by the spirometer fell as

bronchoconstriction developed, from 1.0 arbitrary units/l before histamine challenge to a mean of 0.88 arbitrary units/l (range 0.81-0.95) after maximal bronchoconstriction (Table 12). The same comparisons were made when the inductive plethysmograph was calibrated by a multiple linear regression technique (Chadha et al, 1982; Stradling et al, 1985). Again bronchoconstriction reduced the ratio of the sum of the inductive plethysmograph signal/spirometer volume from 1 arbitrary unit/l to a mean of 0.92 (range 0.87-1.03 arbitrary unit/l). The conclusion is therefore that with both calibration techniques, the inductive plethysmograph may under-estimate tidal volume by some 10% following histamine induced bronchoconstriction.

Data analysis

Breathing patterns and ear oxygen saturation were recorded for between 22 and 83 breaths during each period of the study, with no systematic differences between the number of breaths recorded during each of these periods. Furthermore there was no difference in the number of breaths that were recorded between the histamine and methacholine studies in each patient. Data was recorded on-line using a MINC computer for subsequent off-line analysis. The significance of differences was assessed by paired t test using the Bonferroni correction for multiple comparisons (Miller,

1981). The values are given as mean±SEM.

RESULTS

1. Histamine challenge (Table 13).

The PC_{20} to histamine ranged from 0.05-3.4 mg/dl (mean 0.8mg/dl) (Table 11). On average the FEV_1 fell from 2.99±0.26 to 1.82±0.15 litres, a reduction of 37±11% (Table 13). This was associated with a significant fall in ear oxygen saturation from 95.0±0.4% before the histamine challenge to 91.7±0.8% ($p<0.002$) when this maximal fall in FEV_1 was recorded (Fig 18). The hypoxaemia was not associated with a significant change in "tidal volume"(Vt: 0.40±0.04 before the histamine challenge to 0.44±0.03 litres after the histamine challenge: $0.1>p>0.05$). There was a significant prolongation of breath period (Ttot), caused by prolongation of both inspiratory time [Ti: 1.6±0.2 before the challenge to 2.0±0.2 sec after the challenge ($p<0.04$)] and also of expiratory time [Te: 2.4±0.2 before challenge to 3.1±0.2 sec after challenge ($p<0.02$)]. The minute ventilation ($\dot{V}t/Ttot$) fell significantly following histamine challenge (6.12±0.53 litres before the challenge to 5.37±0.55 l/min after the challenge ($p<0.05$ by a Wilcoxon rank sum test) (Figure 19). However, there was no significant change in either Ti/Ttot or Vt/Ti. Following inhalation of salbutamol there was a significant rise in FEV_1 from 1.82±0.14 to 2.66±0.19 litres ($p<0.02$), and this was

associated with a rise in oxygen saturation from 91.7±0.8% to 95±0.4% ($p<0.002$) (Figure 19). Also following the salbutamol there was a significant shortening of expiratory time which returned towards the control value at 2.2±0.2 sec ($p<0.02$) (Figures 20, 21, and 22).

Methacholine

The PC_{20} to methacholine ranged from 0.04-2.5 mg/dl (mean 0.6mg/dl). FEV_1 fell following methacholine from 2.27±0.21 to 1.62±0.17 litres, (Table 13), an average reduction of 34±11%, very similar to that with histamine challenge. This was associated with a significant fall in oxygen saturation from 95.0±0.5 to 92.5±0.8% ($p<0.02$) (Fig 18). However, there were no significant changes in the breathing pattern following the methacholine challenge (Table 13, Figure 19). Salbutamol inhalation again returned FEV_1 to around the control level, and the ear oxygen saturation also returned from 92.5±0.8% after methacholine challenge to 95.0±0.5% ($p<0.02$) after the salbutamol. However, salbutamol produced no significant change in the breathing pattern following methacholine challenge (Figure 19).

Direct comparison of the changes in breathing and oxygenation produced by histamine with those changes produced by methacholine showed that there were no differences between these agents effects on oxygen saturation, nor or any of the breathing pattern variables.

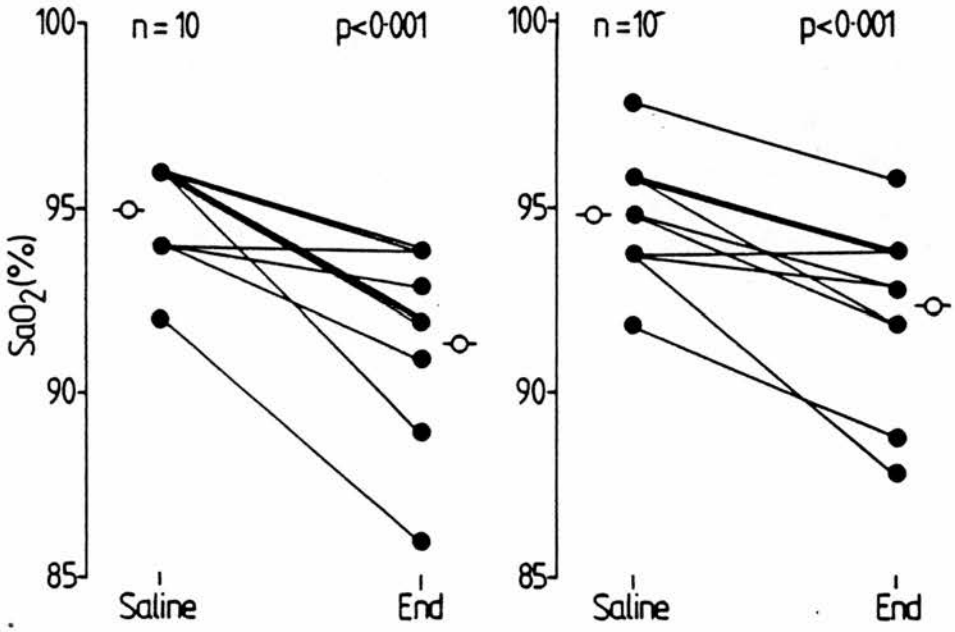

Figure 18 Fall in Sa02 with histamine and methacholine inhalation.

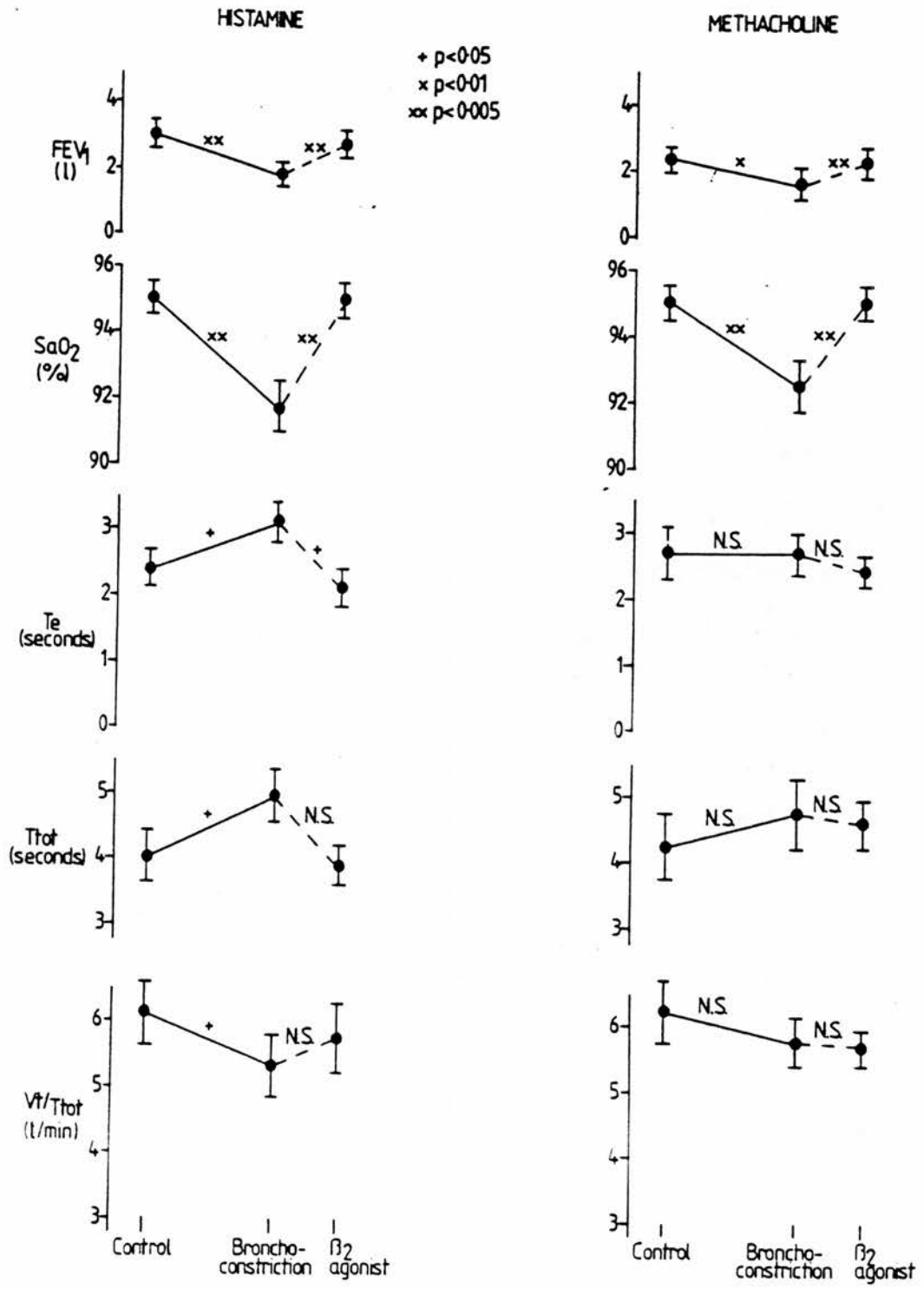

Figure 19 Changes in FEV1, Sa02, expiratory time, breath period and ventilation with histamine and methacholine challenge and their response to bronchodilator. (n=10, mean±SEM).

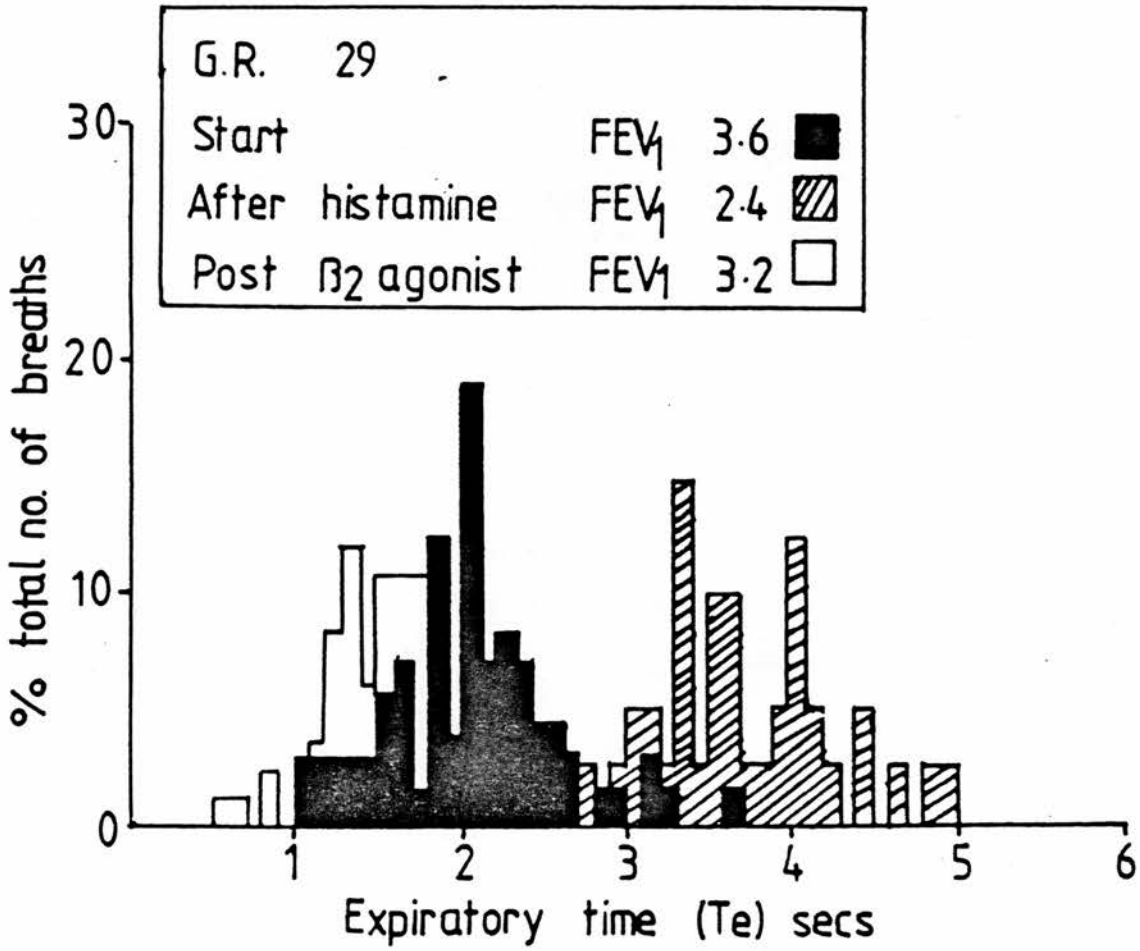

Figure 20 Effect of histamine challenge on expiratory time and response to bronchodilator in one patient.

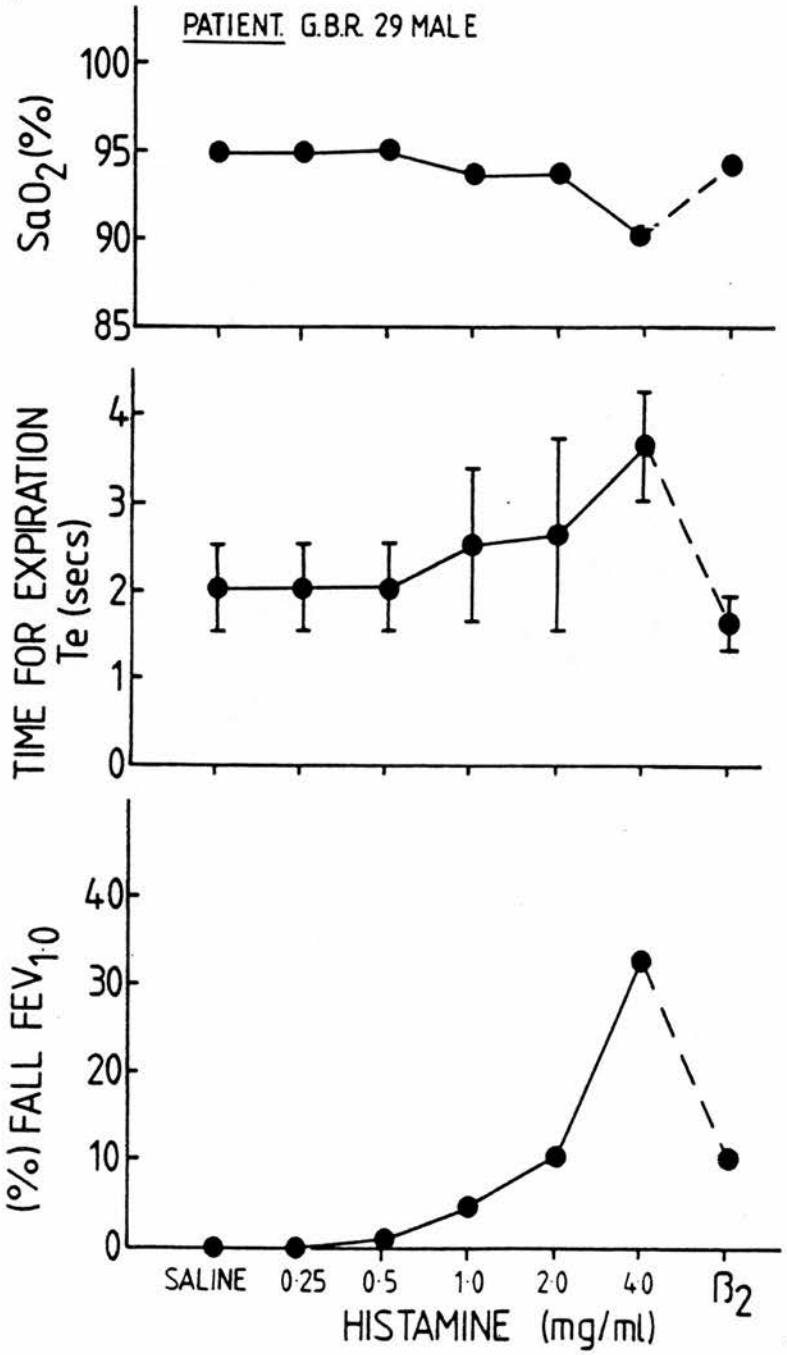

Figure 21 Changes in FEV1, Sa02, and expiratory time in one patient as bronchoconstriction is produced by histamine challenge and its subsequent relief after bronchodilator.

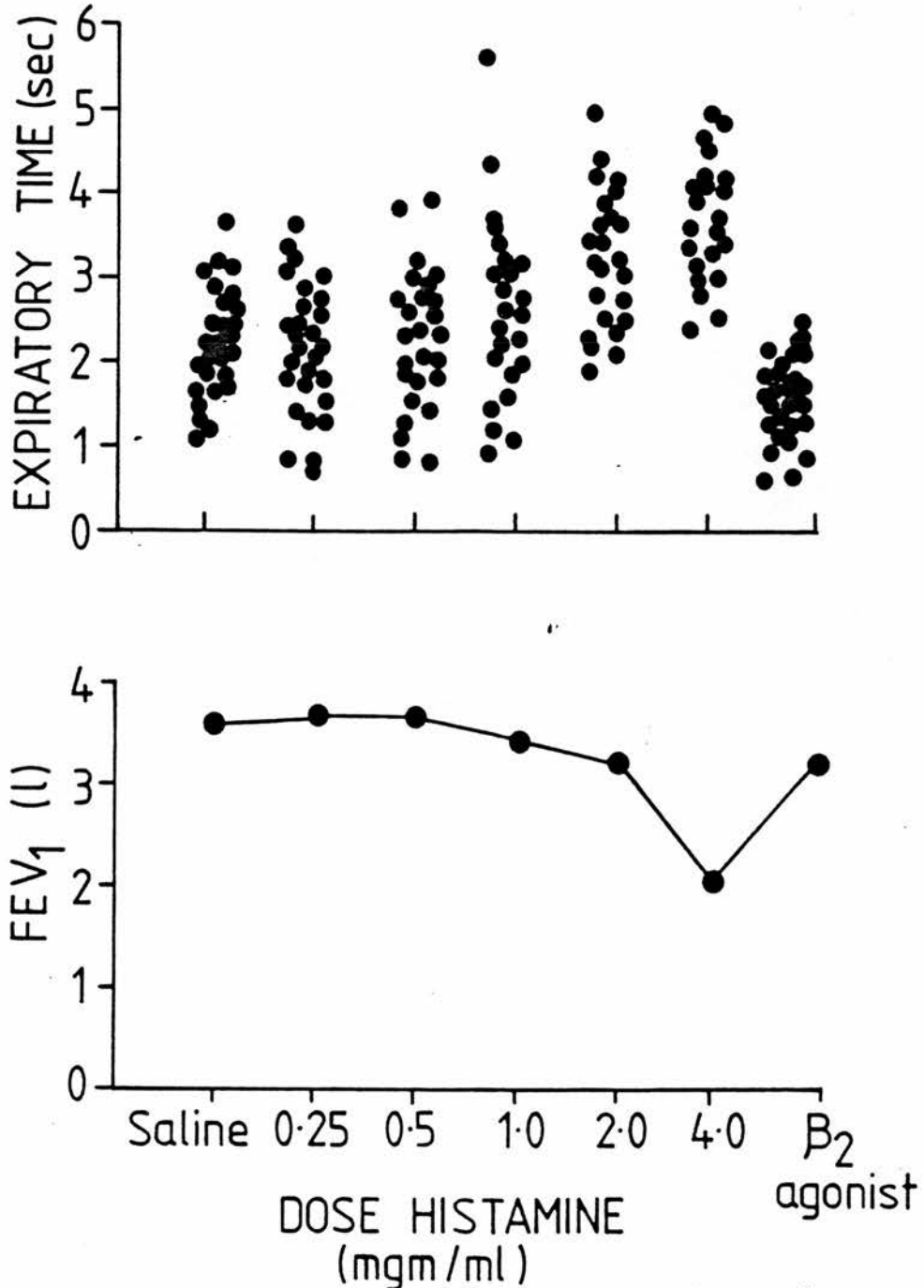

Figure 22 Breath by breath changes in expiratory time and FEV1 during histamine challenge in a stable asthmatic.

DISCUSSION

Thus it has been confirmed that in stable non hypoxaemic asthmatics, bronchoconstriction induced by both histamine and methacholine produced arterial hypoxaemia, and that histamine induced broncho-constriction was associated with an increase in the total breath period (Ttot) but with similar increases in both inspiratory (Ti) and expiratory (Te) times (Figures 20,21 and 22). These changes were reversed when bronchodilatation was induced by inhaling salbutamol.

Each patient's arterial oxygen saturation fell during both challenge procedures. This hypoxaemia was probably not clinically significant in these patients, as the average fall in oxygen saturation was only 3% and the lowest oxygen saturation recorded only being 86%. Nevertheless, this complication of bronchial challenge should be recognised, as a similar degree of bronchoconstriction might induce important hypoxaemia in patients who are more hypoxic before undertaking the challenge, or in those patients who bronchoconstrict to a greater extent during bronchial challenge. The degree of hypoxaemia, as measured by the change in ear oxygen saturation, observed was more than that recorded by Poppius and Stenius (1977) in their 55 patients. Direct comparison of the degree of bronchoconstriction that was induced in the two studies is difficult, as they only recorded peak flow rate, which showed an average fall of 38±15% whereas in this study FEV_1 fell by 37±11%, but

clearly these changes are broadly similar. Their average reduction in $Sa0_2$ of 1.1±1.8%, (which was only a third of that observed in this study) may simply reflect their higher level of oxygen saturation (96.6±0.2%, as compared with a value of 95.0±0.4% in this study). However, the calculated fall in arterial oxygen tension, (assuming an arterial pH of 7.40 and a blood P_{50} of 26.6 mmHg) was similar, being on average in this study 12 mmHg for histamine, and 10mmHg for methacholine, whereas this was 9 mmHg in the study of Poppius and Stenius (1977) of histamine challenge.

The mechanism of the arterial hypoxaemia is not clear from these studies. Overall hypoventilation appears to play some role, at least in the hypoxaemia produced by histamine inhalation, in that that minute ventilation was found to fall ($p<0.05$). However, in contrast there was no significant change in ventilation to accompany the hypoxia produced by methacholine, with a similar degree of bronchoconstriction, nor did ventilation rise when oxygenation improved following the salbutamol inhalation, after either the histamine or methacholine challenges. The failure to observe a fall in ventilation after methacholine challenge is not likely to be a result of the use of the inductive plethysmograph technique, as this device in fact tended to under-estimate the tidal volume changes following induced bronchoconstriction. It thus seems likely that

much of the hypoxaemia resulted from changes in the distribution of alveolar ventilation to perfusion ratios within lung alveoli following bronchoconstriction, but this will clearly need further studies to verify.

There are conflicting results on the effect of bronchoconstriction on breathing patterns. Minute ventilation has been found to increase (Chadha et al, 1984; Kelsen et al, 1981; Hillman et al, 1986; McFadden et al, 1983), to be unchanged (Savoy et al, 1981; Mann et al, 1978; Tobin et al, 1985) or decreased (Pardy et al, 1982) with respiratory frequency increasing (Kelsen et al, 1981; Mann et al, 1978; Pardy et al, 1982) or to be unchanged (Savoy et al, 1981; Tobin et al, 1985). Some of these differences may be due to the use of mouthpieces in many studies (Mann et al, 1978; Savoy et al, 1981, Kelsen et al, 1981; Pardy et al, 1982) which may alter breathing patterns (Gilbert et al, 1972; Askanazi et al, 1980; Douglas et al, 1983, Rodenstein et al, 1985; Perez and Tobin, 1985). Differing severities of bronchoconstriction may also be important as the effect of moderate and severe bronchoconstriction on breathing pattern may be different (McFadden and Austin, 1983; Hillman et al, 1986). Further some of these studies were on normal subjects (Mann et al, 1978, Savoy et al, 1981; Chadha et al, 1984) and some in patients with chronic bronchitis and emphysema (Pardy et al, 1982) and these groups may respond differently to bronchoconstriction. The only directly comparable study

is that of Tobin et al (1985) who studied breathing pattern using an inductive technique following methacholine induced broncho-constriction in asthmatics and found no change in the breathing pattern, in agreement with the results with methacholine in the present study.

The extent of the fall of FEV_1 induced by histamine ($37\pm11\%$) and by methacholine ($34\pm11\%$) were similar, and there were also similar falls in oxygen saturation with both agents. The changes in timing were significant following histamine challenge, but not following methacholine challenge. Nonetheless, if direct comparisons of the changes produced by the two forms of bronchial challenge are made in the same patient, no significant difference between the effects of histamine and the effects of methacholine, on either ear oxygen saturation or on breathing patterns were found. Thus it cannot be deduced that these agents act at different sites in these patients.

With histamine challenge reduction in oxygen saturation and ventilation was found along with changes in respiratory timing. These differ from the changes seen in acute asthma where as bronchodilatation proceeded there was a fall in ventilation and inspiratory drive. There may be several possible reasons for this. Firstly, acute studies were carried out some six hours on average after admission and thus

may have missed changes in respiratory timing. Secondly the severity of bronchoconstriction may influence the breathing pattern (Hillman et al, 1986). The FEV_1 of the stable asthmatics fell on average 37%, but these patients were by no means as acutely distressed as the patients admitted in an acute attack of asthma. Perhaps if bronchoconstriction was induced to produce larger falls in FEV_1 then similar changes would be seen in breathing patterns, but this is clearly ethically and morally indefensible, if not dangerous and cannot even be considered.

It would indeed be of interest, if an acute attack of asthma could be monitored from the stable state through the acute attack and then onto resolution. However, it is obviously technically difficult and time consuming to monitor continuously a stable asthmatic patient, hoping that a spontaneous attack of asthma occurs, so that the changes in breathing pattern can be examined and their response to treatment measured. However, there is a possible way around this problem. Most asthmatics do indeed have recurring spontaneous asthma, which can be observed, namely nocturnal asthma, which can be extremely troublesome even when asthma is stable during daytime. Thus a possibility exists of recording breathing patterns in a stable asthmatic patient who then goes on to experience spontaneous bronchoconstriction during sleep, and this will now be considered in the following chapter.

TABLE 11

BRONCHIAL CHALLENGE: PATIENT DATA

Pat.	Sex	Age (yrs)	Pred. FEV_1 (ℓ)	Actual FEV_1	%fall FEV_1	Pc20mg/ml Histamine
CS	M	28	4.9	3.4	30	0.8
GR	M	29	4.1	3.8	33	2.45
SB	M	18	4.3	2.1	50	0.14
PC	M	17	3.7	1.7	35	0.14
JM	M	60	3.5	1.1	27	0.05
AT	M	47	4.3	2.4	26	0.13
WK	M	50	3.7	3.0	23	3.4
WR	M	42	4.0	2.6	22	0.2
CK	M	21	4.6	2.4	52	0.63
DRS	M	53	3.8	1.9	48	0.05

TABLE 12

COEFFICIENTS OF VARIATION OF THE SLOPE

Subject	Age	Pre/Post Histamine	Breaths	Rib	Abd	Sum	αRib+Abd	αPre	SLOPE Sum	SLOPE αRib+Abd	SLOPE αPre
GR	29	Pre	131	12.74	30.63	13.80	11.09		2.78	7.99	
		Post	119	9.90	27.69	9.65	8.13	8.34	2.63	5.52	8.24
JM	51	Pre	94	21.51	33.76	27.04	21.26		4.48	33.71	
		Post	112	18.25	24.05	19.12	17.23	17.68	3.64	9.47	3.03
WK	44	Pre	80	5.90	9.15	5.16	3.51		8.11	14.78	
		Post	77	8.44	20.61	12.84	7.29	8.37	6.88	23.78	12.80
CS	28	Pre	77	5.21	4.93	3.14	3.12		4.41	5.10	
		Post	86	5.96	13.81	5.64	4.08	5.04	3.81	7.35	4.50

TABLE 13

RESULTS: BRONCHIAL CHALLENGE

	HISTAMINE			METHACHOLINE			
	n = 10	MEAN AND SEM			n = 10	MEAN AND SEM	
FEV_1 (ℓ)	2.99±0.26	1.82±0.14	2.26±0.19	FEV_1 (ℓ)	2.27±0.21	1.62±0.17	2.26±0.21
SaO_2 (%)	95.0±0.4	91.7±0.8	95.0±0.4	SaO_2 (%)	95.0±0.5	92.5±0.8	95.0±0.5
Te (secs)	2.4±0.2	3.1±0.2	2.2±0.2	Te (secs)	2.7±0.4	2.7±0.3	2.4±0.2
Ti (secs	1.6±0.2	2.0±0.2	1.8±0.2	Ti (secs	1.6±0.2	2.2±0.5	2.2±0.4
Ttot (secs)	4.06±0.24	4.94±0.37	3.96±0.24	Ttot (secs)	4.27±0.50	4.79±0.56	4.60±0.6
Ti/Ttot	40±3	41.0±3	45±3	Ti/Ttot	40±2	44±4	45±4
Vt (ℓ)	0.40±0.04	0.44±0.03	0.39±0.04	Vt (ℓ)	0.42±0.04	0.45±0.05	0.42±0.05
Vt/Ttot (ℓ/min)	6.12±0.53	5.37±0.55	5.78±0.50	Vt/Ttot (ℓ/min)	6.25±0.53	5.67±0.38	5.59±0.35
Vt/Ti (ℓ/min)	16.7±2.0	15.5±2.2	14.8±1.8	Vt/Ti (ℓ/min)	17.0±1.8	15.3±1.7	14.1±1.4

CHAPTER 7

The effect of spontaneous bronchoconstriction occurring during sleep on breathing pattern and oxygenation

Patients with asthma often wheeze at night and in the early morning, and this is associated with a reduction in peak expiratory flow rate in the early hours of the morning, the so called "morning dip" (Clark and Hetzel, 1977; Connolly, 1979; Barnes et al, 1980). This symptom may prove difficult to treat (Turner-Warwick, 1977) but this is important as sudden death in asthma tends to occur at these times (Cochrane and Clark, 1971; Hetzel et al, 1977; Lancet editorial, 1983). The causes involved in nocturnal asthma are not fully understood. Three hundred years ago Dr Thomas Willis (1679) believed that nocturnal wheezing was due to overheating of the blood by the bedclothes, whereas Dr John Floyer (1698) himself a sufferer of nocturnal asthma, suggested that wheezing occurred at night "when the nerves are filled with windy spirits".

For more than a century ventilation has been known to be reduced during sleep (Smith, 1860). Subsequent studies confirmed that ventilation was reduced in non rapid eye movement sleep (non REM) (Birchfield et al, 1959; Douglas et al, 1982). Furthermore, because facial instrumentation might alter ventilation, (Gilbert et al,

1972; Askanazi et al, 1980), hypoventilation in non REM sleep has been confirmed in many studies performed without facial instrumentation which showed either decreased thoraco-abdominal movement (Gothe et al, 1981; Skatrud et al, 1981) or arterial hypoxaemia (Doust and Schneider, 1952) and hypercapnia (Bristow et al, 1969). As metabolic rate falls slightly during non REM sleep (White et al, 1983) the hypoxaemia and hypercapnia must reflect hypoventilation.

This hypoxaemia has already been noted in chronic bronchitics (Douglas et al, 1979) and also in chronic stable asthma (Catterall et al, 1982). Furthermore patterns of irregular breathing were noted by Catterall and co-workers (1982) to occur during REM phases of sleep. Thus to study the relationships of breathing pattern to bronchoconstriction in asthma, and to ensure a period of regular breathing, a period of non-REM sleep at the beginning of a nights sleep has been compared to a similar period of non-REM sleep just before waking, in adult asthmatic patients who complained of troublesome nocturnal wheeze.

Methods and Patients

Nine stable asthmatic patients, each complaining of troublesome nocturnal wheeze and/or cough, were studied (Table 14). Each had a greater than 20% increase in FEV_1 following inhalation of 200ug of terbutaline. Five patients were atopic with positive skin tests to grass

pollens, dust or animal dander. None had had exacerbations of asthma for at least six weeks prior to the study. Antihistamines, hypnotics and ketotifen were discontinued at least four weeks prior to the study and the three patients who had previously received either oral theophylline or oral beta-2 agonists, discontinued these drugs at least three weeks prior to the study. All were receiving inhaled beta-2 agonists which were withheld for at least six hours before the study. Patients were also asked to avoid drinks containing caffeine (coffee, cola, cocoa or tea) for six hours before recording as caffeine is a bronchodilator (Becker et al, 1984). None were on sodium cromoglycate and none smoked.

The patients slept in a quiet darkened room on two consecutive nights. The first of these two nights was used to acclimatise the patient to the equipment and surroundings, and only data from the second night was analysed. The patient's peak expiratory flow rate, FEV_1 and FVC were recorded on the study night before sleep and after final awakening before using their inhalers. The following were recorded on an 18 channel recorder (Neuroscribe 180, SLE), running at 15 mm/sec throughout each study night: electroencephalogram from two mid line frontoparietal electrodes, electrooculogram from four electrodes placed outside and above the outer canthi, and electromyogram from two submental electrodes, ear

oxygen saturation (Hewlett Packard 47201A ear oximeter), which was also recorded on a separate recorder (Bryans 28000, Gould Bryans Instruments) running at 0.5 mm/sec, airflow at nose and mouth recorded by thermocouples mounted on nasal prongs. The stages of sleep as measured by electroencephalography were defined by standard criteria (Rechtshaffen and Kales, 1968).

Because of the length of the study and its nature precise measurement of ventilation during sleep, using an inductive plethysmograph in unrestrained subjects may be difficult, due to movement (Zimmerman et al, 1983), or thoraco-abdominal wall phase differences (Tabachnik et al, 1981; Mortolo and Anch, 1978), which may be most marked during episodes of bronchoconstriction (Tobin et al, 1983). In these circumstances two cross sectional areas may not accurately reflect changes in total thoracic volume. Therefore, a simplified calibration was used, as before, setting the ratio of the chest to abdominal signals at one and calibrating the summed output against a wedge spirometer, before and after sleep in the supine posture. In four awake asthmatics this simplified calibration yielded a mean percentage error from Spirometer tidal volume of 9% (range 3-19%) (Morgan et al, 1986), compared to 8% (3-17%) when chest and abdominal gain ratios are determined by multiple regression calibration (Loveridge et al, 1983; Stradling et al, 1985). Data was collected onto a PDP 11/40 computer throughout the study for subsequent off-line

analysis. All subjects gave written informed consent to the study which had the approval of the Hospital Ethical Committee. Results are expressed as mean±SEM. Statistical significance was assessed by the students t test.

Results

On the nights spent in the laboratory, the patients studied all bronchoconstricted significantly, peak expiratory flow rate pre-sleep 301±23 l/min, morning 213±22 l/min ($p<0.01$) thus producing an average fall in peak expiratory flow rate of 29%. The patients slept for 78% of the time in bed, with an average total sleep time of 306±25 minutes. The average number of awakenings during the night was 20±3. Due to technical difficulties the breathing pattern from one patient was not recorded (patient PM) and thus the data on respiratory timing and ventilation refers only to eight patients. However sleep times and oxygen saturation were available on all nine patients.

Breathing patterns early and late in the night were compared by analysing 60-160 breath epochs of Stage 2 sleep during the first and during the last hour of sleep.

Respiratory timing in stage 2 sleep was not significantly different ($p>0.05$) in the first hour of sleep to that during the last hour of sleep (expiratory

time in the first hour 2.3SEM 0.2sec; last hour 2.4±0.2 sec, breath period 4.3±0.2; 4.3±0.2 sec Ti/Ttot 44±3%; 42±2% (Table 15). Furthermore there was again no significance in the variables of tidal volume, inspiratory drive or ventilation.

The mean oxygen saturation when awake was 95.2±0.2% falling to an average lowest oxygen concentration when asleep of 85.8±2.0% (Figure 23). All 9 patients had falls of at least 4% in arterial oxygen saturation (range 4-22%).

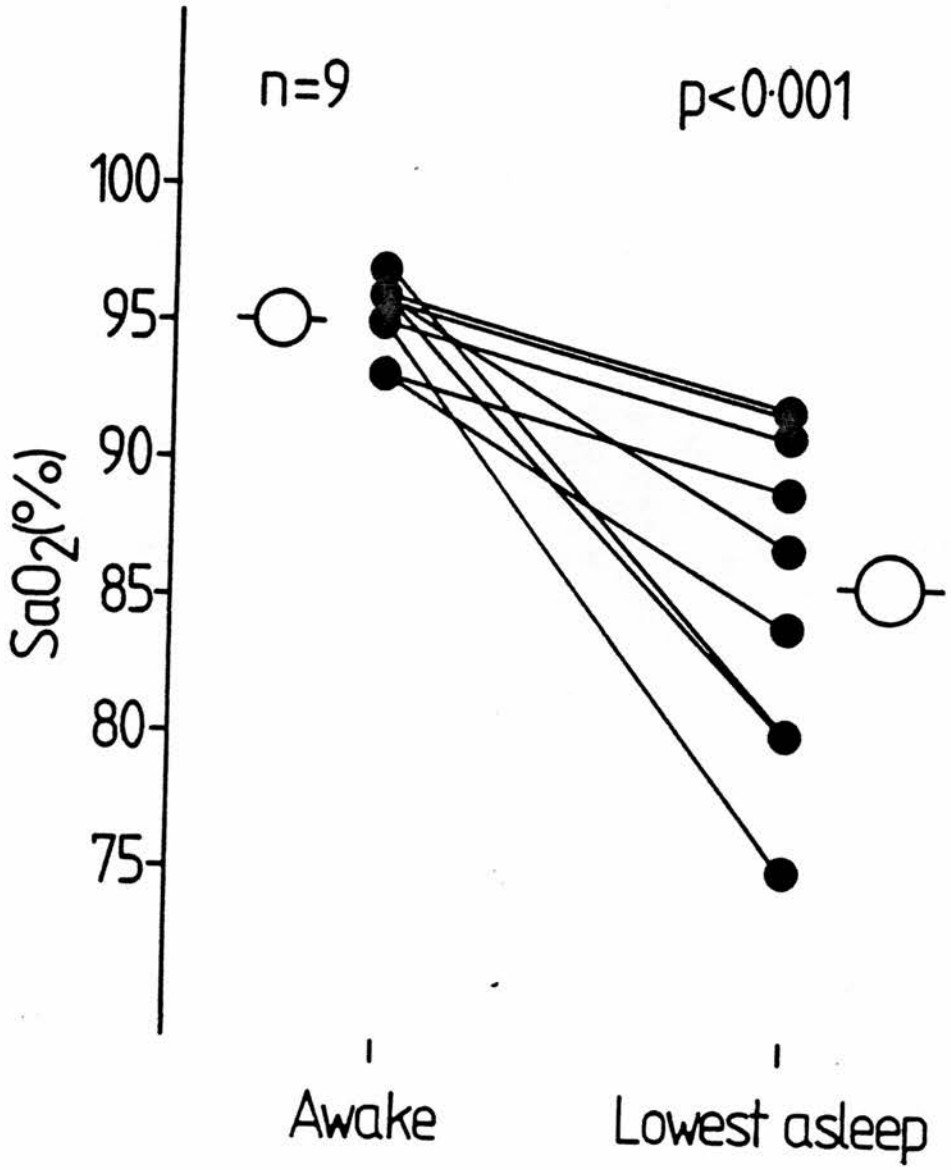

Figure 23 Fall in ear oxygen saturation during sleep.

Discussion

Many asthmatics are troubled by nocturnal cough and wheeze. The cause of this nocturnal bronchoconstriction is unclear, although at least in part it may be caused by sleep itself (Hetzel and Clark 1979; Catterall et al, 1986) and it has been shown that rapid eye movement sleep may contribute to such bronchoconstriction (Shapiro et al, 1986).

In this study no abnormality of breathing pattern in spontaneously sleeping patients with nocturnal asthma, which might indicate the development of nocturnal bronchoconstriction was identified. It has been suggested that expiratory time becomes prolonged in rapid eye movement sleep in asthmatic patients (Catterall et al, 1982) but a more recent study has not shown this (Morgan et al, 1986). Furthermore these same authors looked at Stage 2 sleep early and late and found no significant difference in breathing pattern which is in agreement with the findings in the present study. This inability to find any change in breathing pattern may reflect the relatively mild bronchoconstriction occurring overnight in these patients, as changes in respiratory timing may be more apparent during the moderate or severe bronchoconstriction of acute asthma (Hillman et al, 1986) rather than during mild bronchoconstriction (Tobin et al, 1985; Chadha et al, 1984). This inability to identify an index of nocturnal bronchoconstriction in spontaneously sleeping subjects

is disappointing, as this would have allowed further study of the development of nocturnal asthma without interfering with sleep, either by awakening the patient or by invasive monitoring.

Previous studies have looked at the effect of sleep on breathing patterns compared to wakefulness (Douglas et al, 1982; Rhind et al, 1985). This has been carried out in normal and asthmatic patients. The changes observed in breathing pattern from wakefulness to sleep in asthmatic patients have been similar to those reported in normal subjects. This has also been confirmed by Morgan and co-workers (1986).

It has recently been demonstrated that phase changes occur between the chest and abdomen during acute attacks of asthma in sleeping patients (Issa and Sullivan, 1985). No acute attacks of asthma were observed in this study and phase changes between ribcage and abdomen were not specifically looked for, as interest was centered on trying to identify abnormalities of breathing pattern indicating moderate rather than severe overnight bronchoconstriction.

This study therefore suggests that adults with nocturnal asthma exhibit no specific abnormality indicative of overnight sleep stage 2 related bronchoconstriction. However if spontaneous acute attacks of asthma are monitored in this fashion then further clinical information may become available.

TABLE 14

SLEEP STUDY: PATIENT DATA

Patient	Sex	Age (Yrs)	FEV_1 (ℓ)	Vital Capacity(ℓ)	Treatment (inhaled unless otherwise stated)
AS	M	56	1.8	2.0	B_2Agonist; steroid; oral theophylline
PC	M	54	2.0	4.9	B_2Agonist; steroid; 5mg oral steroid
JM	M	61	2.0	3.3	B_2Agonist; steroid, 10mg oral steroid
MH	F	54	1.5	2.4	B_2Agonist; steroid; oral theophylline
MG	F	65	1.9	2.4	B_2Agonist; steroid; Ipratropium Bromide; 5mg oral steroid; Ketotifen
EF	M	68	1.7	3.8	B_2Agonist; steroid; 7.5mg oral steroid, Terbutaline SA
PM	F	59	2.0	2.3	B_2Agonist; Ipratropium Bromide; 5mg oral steroid
KMcD	F	32	3.0	4.5	B_2Agonist; steroid
WB	M	51	1.9	3.9	B_2Agonist; steroid; Ipratropium Bromide; 10mg oral steroid

TABLE 15

STAGE 2 SLEEP - RESULTS IN 8 PATIENTS

	EARLY	LATE
BREATHS	118	130
Te (secs)	2.3±0.2	2.4±0.2
Ttot (secs)	4.3±0.2	4.3±0.2
Ti/Ttot	44.1±3.6	42.5±2.1
Vt (ℓ)	0.41±0.1	0.5±0.1
Vt/Ttot (ℓ/min)	5.9±1.1	6.6±1.7
Vt/Ti (ℓ/min)	14.5±3.1	16.0±3.6
$Sa0_2$ (%)	93±1.0	92±1.0

CHAPTER 8

SUMMARY

There are numerous methods of measuring ventilation without having a physical connection to the airway. However, most are too complex or are inapplicable in the acute clinical setting. Although this has been overcome by the use of magnetometers, the surface technique of inductive plethysmography is thought to be more accurate and is less likely to show error with changes in posture. Previous methods of measuring ventilation, have used masks or mouthpieces and noseclips, which may themselves change the breathing pattern by increasing tidal volume and reducing frequency. However, it has recently been suggested that it may not be the use of such instrumentation itself, but the obligatory change from nasal to oral route of breathing which may induce the changes observed. Whatever the mechanisms, measurements of ventilation and breathing pattern in the acute clinical setting are rare, as obviously such instrumentation is not well tolerated by an already distressed patient. The use of the respiratory inductive plethysmograph along with an ear oximeter provides a non-invasive method of measuring breathing patterns and oxygen saturation in a patient admitted with an acute respiratory illness.

Ten patients with acute asthma and another ten patients admitted with an acute exacerbation of chronic bronchitis and emphysema were studied initially. They each received standard therapy and the response of treatment recorded. As peak expiratory flow rate rose with the onset of bronchodilatation, the indices of tidal volume, inspiratory drive, and ventilation were seen to fall. This increased ventilation and inspiratory drive are related to bronchoconstriction, as this is relieved, the increased drive and ventilation are no longer required, and thus are reduced. Experiments in dogs have suggested that the increased ventilation in acute asthma may be modified through the vagus. Therefore, it may be that the changes observed occurred via afferent information travelling along the vagus nerves. In contrast in patients with an exacerbation of chronic bronchitis and emphysema, no such changes were recorded and their peak expiratory flow rate also did not change, indicating that these patients do indeed have irreversible airways obstruction.

Thereafter a further 30 patients were studied who were given one of three different treatment regimes. Ten patients received a beta-2 agonist alone, ten patients received an anticholinergic like drug, and ten patients received a combination of the two. Peak expiratory flow rate rose in all three treatment groups, and there was no significant difference between any

treatment group. Again as peak expiratory flow rate rose, there were parallel falls in inspiratory drive, ventilation and tidal volume in all groups. However, although there were falls in inspiratory drive and ventilation with ipratropium this did not reach significance and thus this may further indicate that a beta-2 agonist is the drug of choice in acute asthma, rather than an anticholinergic agent. Furthermore, in ten patients, all from different treatment groups, whose peak expiratory flow rate did not rise significantly, although they were clinically improving, there were parallel falls in inspiratory drive and ventilation. Thus the inductive plethysmograph may be demonstrating changes in breathing pattern before changes can be seen in indices of airway calibre, such as peak expiratory flow rate or FEV_1. Further investigation is required to establish whether these changes in minute ventilation and inspiratory drive are more sensitive than changes in peak expiratory flow rate in monitoring the clinical response in asthma.

The next step was to examine the possibility of recording reciprocal changes in a stable asthmatic, that is an asthmatic patient in whom bronchoconstriction is induced by histamine or methacholine inhalation challenge. This was carried out in ten such patients. In this study increases in expiratory time, inspiratory time and breath period were found in histamine

inhalation. This would be expected as broncho-constriction produces an increased expiratory time. However, no such changes occurred with methacholine and this is in agreement with previous studies by other workers. If direct comparisons of the changes produced by the two forms of bronchial challenge are made in the same patient, there is no significant difference between the effects of histamine and methacholine on ear oxygen saturation or breathing patterns. Thus it cannot be deduced that these agents act at different sites. There are conflicting results on the effects of broncho-constriction on breathing patterns. This may be due to the use of a mouthpiece, or that some of the studies were carried out in normal subjects. However, it is known that differing severities of bronchoconstriction may be important on the effect on breathing pattern. Certainly the stable asthmatic patients broncho-constricted to around 63% of their starting peak expiratory flow rate and certainly were by no means as acutely distressed as the asthmatic patients admitted to the ward. Thus it may be that the difference in severity of broncho-constriction has produced the different breathing patterns observed.

Ear oxygen saturation was found to fall in both histamine and methacholine challenge. This hypoxaemia was not clinically significant, in these patients the average fall being 3% and the largest recorded fall in oxygen saturation was 8%. Nevertheless, this

complication of bronchial challenge should be recognised, as a similar degree of bronchoconstriction might induce important hypoxaemia in patients who were more hypoxic before taking the challenge, or in those patients who bronchoconstrict to a greater extent during bronchial challenge. The mechanism of the arterial hypoxaemia is not clear, overall hypoventilation may play some role, but it seems likely that much of the hypoxaemia may result from changes in distribution of alveolar ventilation to perfusion ratios within lung alveoli following bronchoconstriction.

In attempting to record spontaneous asthma the respiratory inductive plethysmograph was used to record breathing patterns in asthmatic patients who were known to be troubled with nocturnal asthma. They were all found to bronchoconstrict significantly and had hypoxaemic episodes throughout the night. However, no significant change in breathing pattern were recorded from the start of the study, as compared to the end, just before waking, when it would be hoped that they were maximally bronchoconstricted. This inability to find any change in breathing pattern may reflect the relatively mild bronchoconstriction occurring overnight in these patients, as changes in breathing pattern may be more apparent during the moderate or severe bronchoconstriction of acute asthma, rather than during mild bronchoconstriction.

Thus the respiratory inductive plethysmograph allows the recording of respiratory timing and ventilation without the use of face masks or mouth pieces. It can be used in the acute clinical setting and does not interfere with an already distressed patient. With further use of this technique, breathing patterns in acute respiratory illnesses can be recorded and their response to treatment monitored. This may provide valuable clinical information on a patients breathing pattern and identify those patients who require close observation. The respiratory inductive plethysmograph provides a technique where further study of respiratory timing and ventilation is possible and may provide a greater understanding of the factors involved in controlling respiration, both in health and disease.

APPENDIX

The work presented in this thesis was carried out under the supervision of Professor DC Flenley and Dr NJ Douglas of the Department of Respiratory Medicine, City Hospital, Edinburgh. The practical work was carried out by myself and with the technical help of Mrs Anne Parker, Research Physiotherapist, and Mrs Caroline Hoy, Research Technician involved with the sleep studies. The work was carried out during the appointment of Registrar to the Respiratory Medicine Service, Lothian Health Board. During this appointment, however, I was the recipient of an award of a Research Fellowship in Computing experience for one year, funded by the Scottish Home and Health Department.

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